

## WEST Search History





DATE: Thursday, May 04, 2006

Hide?	Set Name	Query	Hit Count
	<i>DB=PGPB,USPT; PLUR=YES; OP=OR</i>		
<input type="checkbox"/>	L17	L13 and humanized adj chimeric adj antibod?	8
<input type="checkbox"/>	L16	humanized adj chimeric adj antibod?	248
<input type="checkbox"/>	L14	L13 and humanized	649
<input type="checkbox"/>	L13	L12 and single adj chain	688
<input type="checkbox"/>	L12	L11 and human	782
<input type="checkbox"/>	L11	L10 and chimeric	782
<input type="checkbox"/>	L10	L7 and monoclonal	1115
<input type="checkbox"/>	L8	L7 and tissue adj factor adj X	4
<input type="checkbox"/>	L7	L6 and tissue adj factor	1258
<input type="checkbox"/>	L6	antibod? and (sepsis or septic adj shock adj syndrome or septic adj shock)	9832
	<i>DB=EPAB,JPAB,DWPI; PLUR=YES; OP=OR</i>		
<input type="checkbox"/>	L5	L4 and tissue adj factor	14
<input type="checkbox"/>	L4	antibod? and (sepsis or septic adj shock adj syndrome or septic adj shock)	984
<input type="checkbox"/>	L3	(tissue adj factor adj X or tissue adj factor adj IX) and (sepsis or septic adj shock adj syndrome or septic adj shock)	0
<input type="checkbox"/>	L2	(tissue adj factor adj X or tissue adj factor adj IX) and antibody and (sepsis or septic adj shock adj syndrome or septic adj shock)	0
	<i>DB=PGPB,USPT; PLUR=YES; OP=OR</i>		
<input type="checkbox"/>	L1	(tissue adj factor adj X or tissue adj factor adj IX) and antibody and (sepsis or septic adj shock adj syndrome or septic adj shock)	4

END OF SEARCH HISTORY

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NEWS	4	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
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NEWS	16	MAR 01	INSPEC reloaded and enhanced
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NEWS	18	MAR 08	X.25 communication option no longer available after June 2006
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NEWS	21	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
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NEWS	25	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected
NEWS EXPRESS			FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT <a href="http://download.cas.org/express/v8.0-Discover/">http://download.cas.org/express/v8.0-Discover/</a>
NEWS HOURS			STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 13:44:21 ON 04 MAY 2006

=> file medline embase biosis caplus  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.84	0.84

FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 13:46:42 ON 04 MAY 2006

FILE 'EMBASE' ENTERED AT 13:46:42 ON 04 MAY 2006  
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=> s (tissue(w)factor(w)X or tissue(w)factor(w)IX) and antibod?  
L1 1 (TISSUE(W) FACTOR(W) X OR TISSUE(W) FACTOR(W) IX) AND ANTIBOD?

=> s (tissue(w)factor(w) and antibod?  
MISSING TERM 'W) AND'  
The search profile that was entered contains a logical operator followed immediately by another operator.

=> s tissue(w)factor and antibod?  
L2 3747 TISSUE(W) FACTOR AND ANTIBOD?

=> s l2 and (sepsis or septic(w)shock(w)syndrome or septic(w)shock)  
L3 213 L2 AND (SEPSIS OR SEPTIC(W) SHOCK(W) SYNDROME OR SEPTIC(W) SHOCK)

=> s l3 and monoclonal  
L4 99 L3 AND MONOCLONAL

=> s l3 and (monoclonal or chimeric or humanized or single(w)chain)

=> dup rem 15  
 PROCESSING COMPLETED FOR L5  
 L6 65 DUP REM L5 (34 DUPLICATES REMOVED)

=> dis ibib abs 50-65

L6 ANSWER 50 OF 65 MEDLINE on STN DUPLICATE 7  
 ACCESSION NUMBER: 95339697 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7614818  
 TITLE: Plasminogen activator and plasminogen activator inhibitor I release during experimental endotoxaemia in chimpanzees: effect of interventions in the cytokine and coagulation cascades.  
 AUTHOR: Biemond B J; Levi M; Ten Cate H; Van der Poll T; Buller H R; Hack C E; Ten Cate J W  
 CORPORATE SOURCE: Centre for Haemostasis, Thrombosis, Atherosclerosis and Inflammation Research, University of Amsterdam, The Netherlands.  
 SOURCE: Clinical science (London, England : 1979), (1995 May) Vol. 88, No. 5, pp. 587-94. Journal code: 7905731. ISSN: 0143-5221.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199508  
 ENTRY DATE: Entered STN: 5 Sep 1995  
 Last Updated on STN: 6 Feb 1998  
 Entered Medline: 22 Aug 1995

AB 1. Disseminated intravascular coagulation frequently accompanies Gram-negative sepsis and may contribute to widespread deposition of microthrombi. Besides the endotoxin-induced activation of coagulation, an important role for the fibrinolytic system has been postulated. The precise mechanisms underlying these fibrinolytic changes during endotoxaemia are not known but have been suggested to be mediated directly by cytokines or secondary to thrombin generation. 2. In the present study we have delineated in detail the fibrinolytic response to a bolus injection of endotoxin in non-human primates and analysed the contribution of cytokines and thrombin generation to the endotoxin-induced release of tissue-type plasminogen activator and plasminogen activator inhibitor 1. Chimpanzees received a bolus injection of endotoxin alone or in combination with blocking monoclonal antibodies directed against tumour necrosis factor or interleukin 6 or in combination with pentoxifylline. Furthermore, to assess the effect of coagulation activation on the activation of fibrinolysis, another group of chimpanzees received endotoxin in combination with either anti-tissue factor antibodies or recombinant hirudin. 3. Infusion of endotoxin induced a rapid increase in plasminogen activator activity and tissue-type plasminogen activator antigen levels and subsequent plasmin generation, reaching peak levels 2h after endotoxin administration. Plasminogen activator inhibitor 1 levels remained constant for the first 2 h, after which time a steep increase was observed. Plasminogen activator activity and plasmin generation decreased simultaneously with the rise in plasminogen activator inhibitor 1 levels. Fibrinolytic activity remained suppressed during the remainder of the study owing to sustained increased levels of plasminogen activator inhibitor 1. The administration of pentoxifylline strongly attenuated the release of tissue-type plasminogen activator and plasminogen activator inhibitor 1, whereas the antitumour necrosis factor antibodies blocked the fibrinolytic response entirely. In contrast, interleukin 6-neutralizing antibodies did not affect the fibrinolytic

response. Although endotoxin-induced generation of thrombin was completely prevented by the administration of **tissue factor-neutralizing antibodies** or by hirudin, no effect on the fibrinolytic response was observed. (ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 51 OF 65 MEDLINE on STN DUPLICATE 8  
ACCESSION NUMBER: 95313005 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7792734  
TITLE: Complete inhibition of endotoxin-induced coagulation activation in chimpanzees with a monoclonal Fab fragment against factor VII/VIIa.  
AUTHOR: Biemond B J; Levi M; ten Cate H; Soule H R; Morris L D; Foster D L; Bogowitz C A; van der Poll T; Buller H R; ten Cate J W  
CORPORATE SOURCE: Center for Hemostasis, Thrombosis, Atherosclerosis and Inflammation Research, University of Amsterdam, The Netherlands.  
SOURCE: Thrombosis and haemostasis, (1995 Feb) Vol. 73, No. 2, pp. 223-30.  
Journal code: 7608063. ISSN: 0340-6245.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199507  
ENTRY DATE: Entered STN: 7 Aug 1995  
Last Updated on STN: 6 Feb 1998  
Entered Medline: 27 Jul 1995

AB Gram-negative **sepsis** is oftentimes complicated by activation of coagulation with disseminated intravascular coagulation and microthrombosis. This may contribute to the associated morbidity, multiple organ failure and death. Recent studies have established that the **tissue factor-dependent** pathway of blood coagulation has a significant participatory role in the initial endotoxin-induced activation of coagulation. **Tissue factor** (TF), expressed on the surface of activated monocytes and endothelial cells forms cell surface complexes with free circulating factors VII and VIIa. The latter complex proteolytically activates factors X and IX. Recent in vivo experiments have shown that a rapidly neutralizing TF **monoclonal antibody** prevents and arrests the endotoxin-induced activation of coagulation and similar studies have shown to reduce mortality in baboons. In this study we describe the preparation of a factor VII/VIIa neutralizing **monoclonal Fab** fragment and characterize its effect on in vivo activation of coagulation during experimental endotoxemia in chimpanzees. Four chimpanzees received a bolus intravenous injection of 4 ng/kg endotoxin in combination with Fab fragments of a factor VII/VIIa neutralizing murine **monoclonal antibody** (12D10) at a dose of either 50 micrograms/kg (n = 2) or 100 micrograms/kg (n = 2). Four control animals received a bolus injection of endotoxin alone. Administration of the 12D10 Fab fragments, immediately preceding the endotoxin bolus injection, effectively blocked the endotoxin-induced activation of coagulation. Plasma levels of products of in vivo activation, namely F1 + 2, TAT complexes and FpA remained at baseline values. The administration of 12D10 resulted in a rapid decline in factor VII/VIIa antigen levels which remained below 5 ng/ml for 180-240 min, followed by a rapid return to baseline levels. (ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 52 OF 65 MEDLINE on STN DUPLICATE 9  
ACCESSION NUMBER: 95375145 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7647218  
TITLE: **Tissue factor** antigen levels in various

biological fluids.

AUTHOR: Fareed J; Callas D D; Hoppensteadt D; Bermes E W Jr  
CORPORATE SOURCE: Department of Pathology, Loyola University Medical Center,  
Maywood, IL 60153, USA.  
SOURCE: Blood coagulation & fibrinolysis : an international journal  
in haemostasis and thrombosis, (1995 Jun) Vol. 6 Suppl 1,  
pp. S32-6.  
Journal code: 9102551. ISSN: 0957-5235.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199509  
ENTRY DATE: Entered STN: 5 Oct 1995  
Last Updated on STN: 5 Oct 1995  
Entered Medline: 28 Sep 1995

AB **Tissue factor** (TF), a transmembrane surface protein, is known to initiate thrombogenesis through plasmatic and cellular activation processes. Besides complexing with factor VII, eventually leading to fibrin generation via the extrinsic pathway, TF can also activate factor IX, resulting in the intrinsic activation of coagulation. Other functions of TF are currently unknown, although various cells are believed to have TF receptors. Many of the post-surgical and post-interventional thrombotic events are due to the release of TF. Increased levels of TF are associated with several pathologic conditions such as cancer, sepsis and inflammation. Cellular necrosis also results in an increase of TF as the cells in the traumatized area lyse and release endogenous cell surface-bound TF. An ELISA method (American Diagnostica, Greenwich, CT) has been developed to assay TF antigen levels in various biological fluids. This ELISA employs a murine monoclonal antibody raised against native human TF for antigen capture. In this study, cerebrospinal fluid, peritoneal fluid, pleural effusion and urine from patients were assayed for their TF content using this ELISA method. Normal individual serum and plasma were also assayed as controls against which the levels of TF in the patients' body fluids could be compared. The amount of TF antigen in normal human plasma and serum was 165 +/- 139 pg/ml and 165 +/- 110 pg/ml, respectively. Concentrations of TF antigen in other fluids were: cerebrospinal fluid 868 +/- 721 pg/ml, peritoneal fluid 124 +/- 247 pg/ml, pleural effusion 385 +/- 569 pg/ml, synovial fluid 97 +/- 23 pg/ml, seminal plasma 11,485 +/- 875 pg/ml and urine 86 +/- 57 pg/ml. (ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 53 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 95191268 EMBASE  
DOCUMENT NUMBER: 1995191268  
TITLE: **Tissue factor** antigen levels in various  
biological fluids.  
AUTHOR: Fareed J.; Callas D.D.; Hoppensteadt D.; Bermes Jr. E.W.  
CORPORATE SOURCE: Department of Pathology, Loyola University Medical Center,  
2160 South First Avenue, Maywood, IL 60153, United States  
SOURCE: Blood Coagulation and Fibrinolysis, (1995) Vol. 6, No.  
SUPPL. 1, pp. S32-S36. .  
ISSN: 0957-5235 CODEN: BLFIE7  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 025 Hematology  
029 Clinical Biochemistry  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 18 Jul 1995  
Last Updated on STN: 18 Jul 1995

AB **Tissue factor** (TF), a transmembrane surface protein, is known to initiate thrombogenesis through plasmatic and cellular

activation processes. Besides complexing with factor VII, eventually leading to fibrin generation via the extrinsic pathway, TF can also activate factor IX, resulting in the intrinsic activation of coagulation. Other functions of TF are currently unknown, although various cells are believed to have TF receptors. Many of the post-surgical and post-interventional thrombotic events are due to the release of TF. Increased levels of TF are associated with several pathologic conditions such as cancer, sepsis and inflammation. Cellular necrosis also results in an increase of TF as the cells in the traumatized area lyse and release endogenous cell surface-bound TF. An ELISA method (American Diagnostica, Greenwich, CT) has been developed to assay TF antigen levels in various biological fluids. This ELISA employs a murine monoclonal antibody raised against native human TF for antigen capture. In this study, cerebrospinal fluid, peritoneal fluid, pleural effusion and urine from patients were assayed for their TF content using this ELISA method. Normal individual serum and plasma were also assayed as controls against which the levels of TF in the patients' body fluids could be compared. The amount of TF antigen in normal human plasma and serum was  $165 \pm 139$  pg/ml and  $165 \pm 110$  pg/ml, respectively. Concentrations of TF antigen in other fluids were: cerebrospinal fluid  $868 \pm 721$  pg/ml, peritoneal fluid  $124 \pm 247$  pg/ml, pleural effusion  $385 \pm 569$  pg/ml, synovial fluid  $97 \pm 23$  pg/ml, seminal plasma  $11485 \pm 875$  pg/ml and urine  $86 \pm 57$  pg/ml. These results show that this ELISA-based assay is capable of quantitating levels of TF in various biological fluids. This method can also be used to detect the presence of TF in cell cultures, organ washes, tissue exudates and extracts. Needle biopsies and body secretions may provide an additional diagnostic parameter in the assessment of various pathophysiologic disorders.

L6 ANSWER 54 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1994:528765 CAPLUS

DOCUMENT NUMBER: 121:128765

TITLE: Human tissue factor heavy chain and fragments and monoclonal antibodies and their therapeutic use

INVENTOR(S): Edgington, Thomas S.; Colman, Robert W.; Kappelmayer, Janos; Edmunds, L. Henry, Jr.; Bernabei, Alvise

PATENT ASSIGNEE(S): Scripps Research Institute, USA; University of Pennsylvania; Temple University

SOURCE: PCT Int. Appl., 155 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9411029	A1	19940526	WO 1993-US11239	19931116
W: AU, CA, FI, JP, NO				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5437864	A	19950801	US 1992-977281	19921116
AU 9456715	A1	19940608	AU 1994-56715	19931116
PRIORITY APPLN. INFO.:			US 1992-977281	A 19921116
			US 1987-33047	B2 19870331
			US 1987-67103	A2 19870625
			US 1988-165939	A2 19880309
			WO 1993-US11239	W 19931116

AB Human tissue factor is identified as a heterodimer of a light and a heavy chain and heavy chain binding site polypeptide analogs and monoclonal antibodies for use as anticoagulants, e.g. in extracorporeal circulation are also described. Heavy chain is manufactured by expression of a cloned cDNA. The protein was purified from human brain by solvent extraction and affinity chromatog. against immobilized

factor VII/VIIa and the protein found to have a 47 kDa heavy chain and an 12.5 kDa light chain. N-terminal sequencing showed that the heavy chain had two different N-termini arising from the loss of two N-terminal amino acids; the small subunit was identified as  $\alpha$ -globin. Polyclonal and monoclonal antibodies were raised against the heavy chain and used in its immunoaffinity purification of the factor and as coagulation inhibitors and were found to be useful in the treatment of shock due to sepsis caused by Gram-neg. bacteria. Peptides derived from the heavy chain were also shown to inhibit factor VII/VIIa-dependent blood clotting. Expression of a gene for the heavy chain and bacterial, yeast, and animal cells is described.

L6 ANSWER 55 OF 65 MEDLINE on STN DUPLICATE 10  
ACCESSION NUMBER: 94220696 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7513203  
TITLE: Monocyte tissue factor induction by lipopolysaccharide (LPS): dependence on LPS-binding protein and CD14, and inhibition by a recombinant fragment of bactericidal/permeability-increasing protein.  
AUTHOR: Meszaros K; Aberle S; Dedrick R; Machovich R; Horwitz A; Birr C; Theofan G; Parent J B  
CORPORATE SOURCE: XOMA Corp, Berkeley, CA 94710.  
SOURCE: Blood, (1994 May 1) Vol. 83, No. 9, pp. 2516-25.  
Journal code: 7603509. ISSN: 0006-4971.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199406  
ENTRY DATE: Entered STN: 13 Jun 1994  
Last Updated on STN: 3 Feb 1997  
Entered Medline: 1 Jun 1994

AB Mononuclear phagocytes, stimulated by bacterial lipopolysaccharide (LPS), have been implicated in the activation of coagulation in sepsis and endotoxemia. In monocytes LPS induces the synthesis of tissue factor (TF) which, assembled with factor VII, initiates the blood coagulation cascades. In this study we investigated the mechanism of LPS recognition by monocytes, and the consequent expression of TF mRNA and TF activity. We also studied the inhibition of these effects of LPS by rBPI23, a 23-kD recombinant fragment of bactericidal/permeability increasing protein, which has been shown to antagonize LPS in vitro and in vivo. Human peripheral blood mononuclear cells, or monocytes isolated by adherence, were stimulated with Escherichia coli O113 LPS at physiologically relevant concentrations ( $>$  or  $=$  10 pg/mL). The effect of LPS was dependent on the presence of the serum protein LBP (lipopolysaccharide-binding protein), as shown by the potentiating effect of human recombinant LBP or serum. Furthermore, recognition of low amounts of LPS by monocytes was also dependent on CD14 receptors, because monoclonal antibodies against CD14 greatly reduced the LPS sensitivity of monocytes in the presence of serum or rLBP. Induction of TF activity and mRNA expression by LPS were inhibited by rBPI23. The expression of tumor necrosis factor showed qualitatively similar changes. Considering the involvement of LPS-induced TF in the potentially lethal intravascular coagulation in sepsis, inhibition of TF induction by rBPI23 may be of therapeutic benefit.

L6 ANSWER 56 OF 65 MEDLINE on STN DUPLICATE 11  
ACCESSION NUMBER: 94289431 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7517185  
TITLE: Role of the lipopolysaccharide (LPS)-binding protein/CD14 pathway in LPS induction of tissue factor expression in monocytic cells.  
AUTHOR: Steinemann S; Ulevitch R J; Mackman N  
CORPORATE SOURCE: Department of Immunology, Scripps Research Institute, La



Jolla, CA 92037.  
 CONTRACT NUMBER: GM 08172 (NIGMS)  
 GM 28485 (NIGMS)  
 HL-48872 (NHLBI)  
 +  
 SOURCE: Arteriosclerosis and thrombosis : a journal of vascular  
 biology / American Heart Association, (1994 Jul) Vol. 14,  
 No. 7, pp. 1202-9.  
 Journal code: 9101388. ISSN: 1049-8834.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199408  
 ENTRY DATE: Entered STN: 15 Aug 1994  
 Last Updated on STN: 3 Feb 1997  
 Entered Medline: 3 Aug 1994

AB Endotoxic shock is associated with a coagulopathy, organ failure, and  
 death. Tissue factor (TF) expression by monocytes  
 exposed to bacterial endotoxin (lipopolysaccharide [LPS]) may mediate the  
 coagulopathy and contribute to the high mortality of this disease. We  
 examined the role of the LPS-binding protein (LBP)/CD14 receptor pathway  
 in the LPS induction of TF expression in human monocytic THP-1 cells and  
 peripheral blood monocytes. In THP-1 cells, the threshold concentration  
 of LPS required to induce TF activity in serum-free medium was reduced  
 20-fold by purified LBP, which also enhanced TF mRNA synthesis.  
 Similarly, monocytes cultured in the presence of serum were induced to  
 express TF antigen at LPS concentrations 100 times lower than monocytes  
 cultured in serum-free medium. An anti-LBP monoclonal  
 antibody indicated that this effect was dependent on the presence  
 of LBP in serum. LPS/LBP induction of TF activity and TF antigen  
 expression in these monocytic cells were also inhibited by an anti-CD14  
 monoclonal antibody, indicating a requirement for the  
 CD14 receptor. Thus, we suggest that low levels of LPS (5 to 100 pg/mL)  
 present during sepsis induce TF expression in monocytes via the  
 LBP/CD14-dependent pathway.

L6 ANSWER 57 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 1994:69600 CAPLUS  
 DOCUMENT NUMBER: 120:69600  
 TITLE: A method for using lipoprotein-associated coagulation  
 inhibitor (LACI) to treat inflammation, including  
 sepsis or septic shock  
 INVENTOR(S): Creasey, Abba A.  
 PATENT ASSIGNEE(S): Cetus Oncology Corp., USA  
 SOURCE: PCT Int. Appl., 54 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
WO 9324143	A1	19931209	WO 1993-US3860	19930423
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 643585	A1	19950322	EP 1993-910775	19930423
EP 643585	B1	19991215		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07507300	T2	19950810	JP 1993-500530	19930423
AT 187648	E	20000115	AT 1993-910775	19930423
ES 2139658	T3	20000216	ES 1993-910775	19930423
PT 643585	T	20000531	PT 1993-910775	19930423

GR 3032779	T3	20000630	GR 2000-400481	20000228
JP 2004210801	A2	20040729	JP 2004-124804	20040420
PRIORITY APPLN. INFO.:			US 1992-891947	A 19920601
			US 1993-4505	A 19930113
			JP 1994-500530	A3 19930423
			WO 1993-US3860	W 19930423

AB A method for prophylactically or therapeutically treating inflammation, including sepsis or septic shock, comprises administration of a therapeutically effective amount of LACI. Inhibition of sepsis by LACI was tested in human umbilical vein endothelial cells using LPS as an inducer of sepsis, as well as in baboons receiving an i.v. Escherichia coli infusion.

L6 ANSWER 58 OF 65 MEDLINE on STN DUPLICATE 12  
 ACCESSION NUMBER: 94052197 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7694295  
 TITLE: Cell-free pool of CD14 mediates activation of transcription factor NF-kappa B by lipopolysaccharide in human endothelial cells.  
 AUTHOR: Read M A; Cordle S R; Veach R A; Carlisle C D; Hawiger J  
 CORPORATE SOURCE: Department of Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN 37232.  
 CONTRACT NUMBER: HL-30647 (NHLBI)  
 HL-30648 (NHLBI)  
 T32-07186  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1993 Nov 1) Vol. 90, No. 21, pp. 9887-91.  
 Journal code: 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199312  
 ENTRY DATE: Entered STN: 17 Jan 1994  
 Last Updated on STN: 29 Jan 1996  
 Entered Medline: 9 Dec 1993

AB Lipopolysaccharide (LPS), a major envelope component of Gram-negative bacteria, is the most frequent causative agent of septic shock and disseminated intravascular coagulation. LPS activates both CD14-positive (monocytes, macrophages, polymorphonuclear leukocytes) and CD14-negative (B-cell lines, endothelial cells) cells. CD14, a 55-kDa glycosyl-phosphatidylinositol-anchored membrane protein present on mature myeloid cells, serves as a receptor for LPS in complex with a soluble (serum-derived) LPS-binding protein (LBP). In this report, we show that human umbilical vein endothelial cells (HUVEC), which do not express measurable CD14 protein, become 3000-fold more sensitive to LPS-induced activation in the presence of serum, as measured by activation of the transcription factor NF-kappa B and expression of mRNA encoding tissue factor, a procoagulant molecule. This enhanced responsiveness of HUVEC is specifically mediated by the cell-free pool of CD14 (soluble CD14, sCD14) found in serum. The role of sCD14 in HUVEC activation by LPS was established by (i) the blocking effect of monoclonal anti-CD14 antibodies which discriminate between cell-bound and sCD14, (ii) the lack of the serum-enhancing effect after immunodepletion of sCD14, and (iii) establishing a reconstituted system in which recombinant sCD14 was sufficient to enhance the effects of LPS in the absence of serum and without a requirement for LBP. Thus, this mechanism of endothelial cell activation by LPS involves a cell-free pool of sCD14 most likely shed from CD14-positive cells of the monocytic lineage.

L6 ANSWER 59 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 93244751 EMBASE  
 DOCUMENT NUMBER: 1993244751  
 TITLE: Pathogenesis of disseminated intravascular coagulation in sepsis.  
 AUTHOR: Levi M.; Ten Cate H.; Van der Poll T.; Van Deventer S.J.H.  
 CORPORATE SOURCE: Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands  
 SOURCE: Journal of the American Medical Association, (1993) Vol. 270, No. 8, pp. 975-979. .  
 ISSN: 0098-7484 CODEN: JAMAAP  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
 006 Internal Medicine  
 025 Hematology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 26 Sep 1993  
 Last Updated on STN: 26 Sep 1993

AB Objective. - To review new insights in the pathogenetic mechanisms involved in the development of disseminated intravascular coagulation (DIC) in septic patients, in order to develop new directions for therapeutic intervention. Data Sources. - Articles and published peer-reviewed abstracts on the mechanism of the initiation of DIC in sepsis. Study Selection. - Studies selected for detailed review were those reporting specifics about the mechanism of activation of coagulation and fibrinolysis in experimental human and animal models of sepsis. Data extraction guidelines for assessing data quality included validity of the model, quality of the laboratory assessment of activation of coagulation and fibrinolysis, and methodological considerations, such as the presence of control experiments and statistical analysis. Data Synthesis. - After the presence of endotoxin in the circulation, significant coagulation activation can be detected. This activation is preceded by an increase in the serum levels of various cytokines, such as tumor necrosis factor and interleukins. Inhibition of the increase in tumor necrosis factor results in inhibition of coagulation activation. Measurement of molecular markers for the activation of coagulation proteins at various levels indicates that the activation of coagulation is mediated by the tissue factor-dependent pathway, which is further confirmed by experiments in which the inhibition of the tissue factor-dependent pathway resulted in complete inhibition of coagulation activation. The activation of coagulation seems to be amplified by impaired function of the protein C-protein S inhibitory pathway. An imbalance between coagulation and fibrinolysis, ultimately leading to plasminogen activator inhibitor type 1-mediated inhibition of fibrinolysis, may further promote the procoagulant state. Conclusion. - The increased knowledge of the various pathogenetic mechanisms of coagulation activation and fibrinolysis in sepsis may have therapeutic implications; however, their efficacy needs to be assessed in appropriate clinical trials.

L6 ANSWER 60 OF 65 MEDLINE on STN DUPLICATE 13  
 ACCESSION NUMBER: 94242913 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7514452  
 TITLE: Antilipid A monoclonal antibody HA-1A decreases the capacity of bacterial lipopolysaccharide to activate human vascular endothelial cells by an immune adherence mechanism.  
 AUTHOR: Paleolog E M; Katsikis P; Harris G; Daddona P; Dalesandro M R; Kinney C S; Woody J N; Feldmann M  
 CORPORATE SOURCE: Kennedy Institute of Rheumatology, Sunley Division, London, UK.  
 SOURCE: Cytokine, (1993 Nov) Vol. 5, No. 6, pp. 570-7.

Journal code: 9005353. ISSN: 1043-4666.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199406  
ENTRY DATE: Entered STN: 29 Jun 1994  
Last Updated on STN: 29 Jan 1996  
Entered Medline: 23 Jun 1994

AB Human monoclonal IgM antibody HA-1A, which recognizes the lipid A component of bacterial lipopolysaccharide (LPS), has been shown to reduce mortality in Gram negative septicemia. The vascular endothelial lining of blood vessels, which controls leucocyte traffic and activation, as well as haemostatic balance, may be one of the primary targets of LPS action during sepsis. In earlier studies we have described HA-1A-induced immune adherence of LPS to complement receptors on erythrocytes, and showed that pre-incubation with HA-1A, in the presence of complement and red blood cells, markedly reduced LPS-induced cytokine production from peripheral blood mononuclear cells. In the present study, we measured the effect of immune adherence of LPS in the presence of HA-1A on the responses of cultured endothelial cells, and found that subsequent expression of adhesion molecules such as E-selectin, ICAM-1 and VCAM-1, and secretion of the cytokines interleukin-6 and granulocyte-macrophage colony stimulating factor were markedly reduced. Moreover, the ability of LPS to increase levels of tissue factor procoagulant activity on endothelial cells was markedly diminished by LPS immune adherence to HA-1A. This decrease in endothelial activation in response to LPS following immune adherence to HA-1A may play a significant role in the protective effect of HA-1A in vivo during the course of Gram negative sepsis.

L6 ANSWER 61 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:630363 CAPLUS  
DOCUMENT NUMBER: 115:230363  
TITLE: Endotoxin-induced thrombosis factor which induces procoagulant activity in epithelial cells  
INVENTOR(S): Gerlach, Herwig; Stern, David  
PATENT ASSIGNEE(S): Columbia University, USA  
SOURCE: PCT Int. Appl., 37 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9113086	A1	19910905	WO 1991-US1277	19910228
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
US 5227368	A	19930713	US 1990-486311	19900228
AU 9175505	A1	19910918	AU 1991-75505	19910228
PRIORITY APPLN. INFO.:			US 1990-486311	A 19900228
			WO 1991-US1277	A 19910228

AB The title factor comprises a protein characterized of by mol. weight 50,000-65,000 Daltons on reduced and nonreduced SDS-PAGE, by maximal recovery at 52,000-58,000 Daltons on elution from the gel, by the ability to migrate as a single, by the ability to precipitate in PEG >15%. The factor maximally induces tissue factor after 6-8 h. Further biochem. properties are described. The factor can be used in the treatment of cancer and Gram-neg. sepsis (no data). Purification and characterization of the title factor from lipopolysaccharide-stimulated marine macrophages is described.

L6 ANSWER 62 OF 65 MEDLINE on STN DUPLICATE 14

ACCESSION NUMBER: 91256409 MEDLINE

DOCUMENT NUMBER: PubMed ID: 2044206

TITLE: Lethal E. coli **septic shock** is prevented by blocking **tissue factor** with **monoclonal antibody**.

AUTHOR: Taylor F B Jr; Chang A; Ruf W; Morrissey J H; Hinshaw L; Catlett R; Blick K; Edgington T S

CORPORATE SOURCE: Oklahoma Medical Research Foundation, Oklahoma City.

CONTRACT NUMBER: P01 HL 16411 (NHLBI)  
R01 GM37704 (NIGMS)  
R01 HL44225 (NHLBI)  
+

SOURCE: Circulatory shock, (1991 Mar) Vol. 33, No. 3, pp. 127-34.  
Journal code: 0414112. ISSN: 0092-6213.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199107

ENTRY DATE: Entered STN: 2 Aug 1991  
Last Updated on STN: 2 Aug 1991  
Entered Medline: 18 Jul 1991

AB Gram-negative bacteremia poses a major health problem, causing one-half of cases of lethal **septic shock** acquired during hospitalization. Bacterial lipopolysaccharide (LPS) and the inflammatory cytokines, tumor necrosis factor (TNF) and interleukin-1 (IL-1), have been shown to be essential mediators of **septic shock**. Among the effects of these mediators is a coagulopathy that may be triggered by induced expression of **tissue factor** (TF) on macrophages and endothelial cells. We now report that 500 micrograms/kg of either immunoglobulin G (IgG) or Fab fragments of a **monoclonal antibody** against TF administered to baboons as a pretreatment attenuates the coagulopathy and protects against LD100 *Escherichia coli*. This study provides direct evidence of an essential effector role for TF in **septic shock**.

L6 ANSWER 63 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1990:255850 BIOSIS

DOCUMENT NUMBER: PREV199038122438; BR38:122438

TITLE: **MONOCLONAL ANTIBODIES AS THERAPEUTIC AGENTS TO BLOCK TISSUE FACTOR THROMBOPLASTIN FUNCTION.**

AUTHOR(S): RUF W [Reprint author]; MORRISSEY J H; EDGINGTON T S

CORPORATE SOURCE: DEP IMMUNOL, RES INST SCRIPPS CLIN, 1066 N TORREY PINES RD, LA JOLLA, CALIF 92037, USA

SOURCE: Blut, (1990) Vol. 60, No. 2, pp. 116.  
Meeting Info.: 6TH CONGRESS OF THE SOCIETY FOR THROMBOSIS AND HEMOSTASIS RESEARCH, KIEL, WEST GERMANY, FEBRUARY 21-24, 1990. BLUT.  
CODEN: BLUTA9. ISSN: 0006-5242.

DOCUMENT TYPE: Conference; (Meeting)

FILE SEGMENT: BR

LANGUAGE: ENGLISH

ENTRY DATE: Entered STN: 23 May 1990  
Last Updated on STN: 31 May 1990

L6 ANSWER 64 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1989:434681 CAPLUS

DOCUMENT NUMBER: 111:34681

TITLE: Human **tissue factor**: gene cloning, polypeptide analogs, **monoclonal antibodies**

INVENTOR(S): Edgington, Thomas S.; Morrissey, James H.  
PATENT ASSIGNEE(S): Scripps Clinic and Research Foundation, USA  
SOURCE: PCT Int. Appl., 143 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8807543	A1	19881006	WO 1988-US998	19880329
W: AU, DK, FI, JP, NO				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
US 5110730	A	19920505	US 1987-67103	19870625
AU 8816274	A1	19881102	AU 1988-16274	19880329
AU 605864	B2	19910124		
EP 309548	A1	19890405	EP 1988-903654	19880329
EP 309548	B1	20030730		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 01503438	T2	19891122	JP 1988-503555	19880329
JP 2809415	B2	19981008		
AT 246200	E	20030815	AT 1988-903654	19880329
EP 1364969	A2	20031126	EP 2003-77335	19880329
EP 1364969	A3	20041229		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
ES 2009590	A6	19891001	ES 1988-1019	19880330
FI 8805543	A	19881129	FI 1988-5543	19881129
FI 100184	B1	19971015		
NO 8805326	A	19890130	NO 1988-5326	19881129
NO 305211	B1	19990419		
DK 8806668	A	19890131	DK 1988-6668	19881129
DK 175703	B1	20050124		
FI 9504347	A	19950915	FI 1995-4347	19950915
FI 97813	B	19961115		
FI 97813	C	19970225		
US 6001978	A	19991214	US 1997-844806	19970422
DK 200401498	A5	20041001	DK 2004-1498	20041001

PRIORITY APPLN. INFO.:

US 1987-33047	A	19870331
US 1987-67103	A	19870625
US 1988-165939	A	19880309
EP 1988-903654	A3	19880329
WO 1988-US998	A	19880329
DK 1988-6668	A	19881129
FI 1988-5543	A	19881129
US 1992-880079	A3	19920429

AB The human **tissue factor** (TF) heavy chain gene is cloned, and human TF binding site polypeptide analogs and **monoclonal antibodies** to human TF and to the binding site analogs are prepared. Using recombinant DNA technol., the cloning vector pSV-huTFh was constructed. This vector contains the human TF gene under the control of SV40 virus sequences. The vector was transfected into CHO cells. Transfected cells were cultured under conditions compatible with cell growth and expression of the recombinant DNA, and the expressed, soluble human TF was harvested from the culture medium by well-known techniques. The human TF so prepared displayed biol. activity, i.e., the ability to bind factor VII/VIIa. **Monoclonal antibodies** to the TF prevented **septic shock** and death in baboons infused with an LD100 of Escherichia coli.

L6 ANSWER 65 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 15

ACCESSION NUMBER: 87013402 EMBASE  
DOCUMENT NUMBER: 1987013402

TITLE: Human platelet aggregation is initiated by peripheral blood mononuclear cells exposed to bacterial lipopolysaccharide in vitro.

AUTHOR: Schwartz B.S.; Monroe M.C.

CORPORATE SOURCE: Department of Medicine, University of Wisconsin, Madison, WI 53706, United States

SOURCE: Journal of Clinical Investigation, (1986) Vol. 78, No. 5, pp. 1136-1141. .

CODEN: JCINAO

COUNTRY: United States

DOCUMENT TYPE: Journal

FILE SEGMENT: 037 Drug Literature Index  
025 Hematology  
004 Microbiology  
005 General Pathology and Pathological Anatomy  
026 Immunology, Serology and Transplantation

LANGUAGE: English

ENTRY DATE: Entered STN: 11 Dec 1991  
Last Updated on STN: 11 Dec 1991

AB Platelet consumption is a prominent feature of disseminated intravascular coagulation. We investigated whether monocyte procoagulant activity (PCA) might play a role in platelet consumption associated with gram-negative septicemia. Human mononuclear cells exposed in vitro to lipopolysaccharide demonstrated parallel dose-dependent increases in PCA and ability to induce platelet aggregation. Induction of platelet aggregation required the generation of thrombin dependent on coagulation Factors VII, X, and II, and calcium. This is consistent with monocyte tissue factor initiating thrombin generation. A specific monoclonal antimonocyte antibody was used to identify monocytes via indirect immunofluorescence, and demonstrated that all monocytes were included in platelet aggregates. Mononuclear cells that did not express PCA did not induce platelet aggregation and monocytes were not surrounded by platelet clumps. These data suggest that monocytes induced to express tissue factor on their surface may be important mediators of endotoxin-induced platelet, as well as fibrinogen, consumption.

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(Y)/N:y

L6 ANSWER 40 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
ACCESSION NUMBER: 2001198323 EMBASE

TITLE: Pediatric sepsis and multiple organ dysfunction syndrome.  
AUTHOR: Despond O.; Proulx F.; Carcillo J.A.; Lacroix J.  
CORPORATE SOURCE: Dr. J. Lacroix, Sainte-Justine Hospital, 3175 Cote Sainte-Catherine, Montreal, Que. H3T 1C5, Canada. jacques\_lacroix@ssss.gouv.qc.ca  
SOURCE: Current Opinion in Pediatrics, (2001) Vol. 13, No. 3, pp. 247-253. .  
Refs: 68  
ISSN: 1040-8703 CODEN: COPEE  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
007 Pediatrics and Pediatric Surgery  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 22 Jun 2001  
Last Updated on STN: 22 Jun 2001

AB Systemic inflammatory response syndrome may be viewed as the systemic expression of cytokine signals that normally function on an autocrine or paracrine level. Sepsis is defined as systemic inflammatory response syndrome caused by an infection. Multiple organ dysfunction syndrome may represent the end stage of severe systemic inflammatory response syndrome or sepsis. Many cells are involved, including endothelial cells and leukocytes and multiple proinflammatory and antiinflammatory mediators (cytokines, oxygen free radicals, coagulation factors, and so forth). Various pathophysiologic mechanisms have been postulated. The most popular theory is that the inflammatory process loses its autoregulatory capacity; however, microcirculatory dysregulation and apoptosis may also be important, and a new paradigm posits a complex nonlinear system. Many new treatments have been studied recently. The usefulness of immune modulating diets remains to be evaluated. Molecular immunomodulation is still of unclear value. The therapy of sepsis and multiple organ dysfunction syndrome remains mainly supportive. .COPYRGT. 2001 Lippincott Williams & Wilkins, Inc.

L6 ANSWER 41 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:323249 CAPLUS  
DOCUMENT NUMBER: 132:329952  
TITLE: Method for using lipoprotein-associated coagulation inhibitor to treat sepsis, septic shock, and inflammation  
INVENTOR(S): Creasey, Abba A.; Broze, George J.  
PATENT ASSIGNEE(S): Washington University, USA; Chiron Corp.  
SOURCE: U.S., 30 pp., Cont.-in-part of U.S. Ser. No. 224,118, abandoned.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6063764	A	20000516	US 1995-472761	19950607
US 2003171292	A1	20030911	US 2003-368000	20030219
JP 2004210801	A2	20040729	JP 2004-124804	20040420
US 2005181993	A1	20050818	US 2004-891493	20040715
PRIORITY APPLN. INFO.:			US 1992-891947	B2 19920601
			US 1992-897135	B2 19920611
			US 1993-4505	B1 19930113
			US 1993-20427	B1 19930222



US 1994-224118	B2 19940329
US 1994-253427	B2 19940602
US 1994-270455	B2 19940705
JP 1994-500530	A3 19930423
US 1995-472761	A1 19950607
US 2000-521180	B1 20000308
US 2001-971362	B1 20011005
US 2003-368000	A1 20030219

AB A method for prophylactically or therapeutically treating **sepsis** or **septic shock** is described, wherein an inhibitor to **tissue factor** is administered to septic patients. Addnl., a method for treating inflammation is described wherein the inhibitor is administered to patients. This inhibitor is termed lipoprotein-associated coagulation inhibitor (LACI). It is 38 kD and has 276 amino acids. LACI has now been shown to be useful for the treatment of **sepsis**, **septic shock** and inflammation. Production of LACI using cloning methodol. is also described.

REFERENCE COUNT: 133 THERE ARE 133 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 42 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:241001 CAPLUS

DOCUMENT NUMBER: 133:2174

TITLE: Measurement of **tissue factor** activity in whole blood

AUTHOR(S): Santucci, Richard A.; Erlich, Jonathan; Labriola, Joanne; Wilson, Mark; Kao, K. J.; Kickler, Thomas S.; Spillert, Charles; Mackman, Nigel

CORPORATE SOURCE: The Scripps Research Institute, La Jolla, CA, 92037-9701, USA

SOURCE: Thrombosis and Haemostasis (2000), 83(3), 445-454  
CODEN: THHADQ; ISSN: 0340-6245

PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB High circulating levels of the procoagulant mol. **tissue factor** (TF) are associated with thrombosis in a variety of diseases including unstable angina, cancer, and **sepsis**. Currently, there are no clin. assays to measure the level of TF activity in whole blood. We present an assay called **Tissue Factor Clotting Time** ("TiFaCT") that detects fibrin formation in human blood. The mean baseline clotting time in a healthy population was  $472 \pm 94$  s (mean  $\pm$  SD,  $n = 150$ ). Bacterial lipopolysaccharide (LPS or endotoxin) shortened the clotting time in a time-dependent manner. Inhibitory anti-TF **antibodies** prolonged the clotting time of LPS-stimulated blood, indicating that the shortened clotting time was due to induction of TF expression. Patients with unstable angina had shortened mean baseline clotting time ( $284 \pm 86$ ,  $n = 13$ ) compared with healthy volunteers ( $474 \pm 98$ ,  $n = 30$ ), suggesting that these patients had elevated levels of circulating TF. The TiFaCT assay should prove clin. useful in quantifying the levels of circulating TF in patients at risk of thrombosis.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 43 OF 65 MEDLINE on STN

DUPLICATE 5

ACCESSION NUMBER: 97341999 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9198199

TITLE: **Tissue factor** pathway inhibitor: potential therapeutic applications.

AUTHOR: Bajaj M S; Bajaj S P

CORPORATE SOURCE: Department of Internal Medicine, Saint Louis University School of Medicine, MO, USA.. BajajMS@wpogate.slu.edu

SOURCE: Thrombosis and haemostasis, (1997 Jul) Vol. 78, No. 1, pp.

471-7. Ref: 69  
Journal code: 7608063. ISSN: 0340-6245.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199708  
ENTRY DATE: Entered STN: 25 Aug 1997  
Last Updated on STN: 25 Aug 1997  
Entered Medline: 8 Aug 1997

AB Tissue factor pathway of coagulation plays a dominant role during normal haemostasis. Tissue factor pathway inhibitor (TFPI), expressed primarily by the microvascular endothelium, appears to be the major physiologic inhibitor of TF-induced coagulation. TF-initiated coagulation also plays an important role in the pathophysiology of many diseases including coronary thrombosis, sepsis, disseminated intravascular coagulation, stroke, cancer, acute respiratory distress syndrome, and ischemia-reperfusion injury. Several animal studies have found a beneficial effect of anti-TF monoclonal antibodies and, recombinant TFPI in some of the above clinical conditions. rTFPI is presently being used in clinical trials in patients with sepsis and in those following microvascular surgery. This article discusses many of the animal studies addressing inhibition of TF-induced coagulation, as well as potential therapeutic uses of rTFPI in humans.

L6 ANSWER 44 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:605041 CAPLUS  
DOCUMENT NUMBER: 127:261610  
TITLE: Effects of recombinant soluble CD14 on association of bacterial lipopolysaccharide with bovine alveolar macrophages in vitro  
AUTHOR(S): Yang, Z.; Lichenstein, H. S.; Bochsler, P. N.  
CORPORATE SOURCE: Department of Pathology, The University of Tennessee, Knoxville, TN, 37901, USA  
SOURCE: Journal of Endotoxin Research (1997), 4(3), 205-213  
CODEN: JENREB; ISSN: 0968-0519  
PUBLISHER: Churchill Livingstone  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The CD14 receptor on the cell membrane of macrophages is well-known as a receptor for bacterial lipopolysaccharide (LPS) and contributes to cellular activation, but the potential role of the soluble CD14 receptor (sCD14) in macrophage activation is less understood. In this study, CD14-dependent binding or uptake of [3H]-LPS by bovine alveolar macrophages (AM) was determined in vitro, and LPS-mediated activation of AM was evaluated using the tissue factor-procoagulant assay. In the absence of LPS-binding protein (LBP) or other serum components, recombinant human sCD14 (rsCD14) enhanced binding of [3H]-LPS to AM and also increased LPS-mediated activation of AM in a concentration-dependent manner.

These effects were inhibitable by anti-CD14 monoclonal antibodies; the antibodies decreased, but did not completely prevent, association of [3H]-LPS with cells. Binding of [3H]-LPS to AM was greater in the presence of rsCD14 + bovine LBP (5-40 ng/mL), as compared to the moderately lower quantity of bound lipopolysaccharide with [3H]-LPS + LBP alone, or compared to the much lower quantity of lipopolysaccharide bound when [3H]-LPS was used alone. In the presence of whole serum, the effects of rsCD14 were dichotomous and depended upon the serum concentration. RsCD14 (4 µg/mL) added to medium containing ≥ 1% (volume/volume) fetal bovine serum resulted in reduced binding/uptake of [3H]-LPS by AM. However, rsCD14 slightly enhanced binding of [3H]-LPS to AM at a very low concentration of serum (0.1%) and in the absence of serum.

These results suggest that sCD14 enhances binding of [3H]-LPS to macrophages when serum-deficient conditions prevail, and sCD14 also enhances binding of LPS in the presence of low concns. of purified LBP. However, sCD14 decreases association of LPS with AM in the presence of serum ( $\geq 1\%$ ).

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 45 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:295080 CAPLUS

DOCUMENT NUMBER: 124:325361

TITLE: Chimeric proteins and muteins of tissue factor pathway inhibitors TFPI and TFPI-2

INVENTOR(S): Innis, Michael A.; Creasey, Alba A.

PATENT ASSIGNEE(S): Chiron Corporation, USA

SOURCE: PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604378	A2	19960215	WO 1995-US9464	19950725
WO 9604378	A3	19960314		
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5589359	A	19961231	US 1994-286521	19940805
US 5563123	A	19961008	US 1995-437841	19950509
US 5696088	A	19971209	US 1995-436175	19950509
CA 2196290	AA	19960215	CA 1995-2196290	19950725
AU 9531500	A1	19960304	AU 1995-31500	19950725
AU 710535	B2	19990923		
EP 776366	A1	19970604	EP 1995-927478	19950725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10503375	T2	19980331	JP 1996-506598	19950725
US 6174721	B1	20010116	US 1997-943682	19971014
US 2002197667	A1	20021226	US 2000-741106	20001221
US 6783960	B2	20040831		
US 2005008654	A1	20050113	US 2004-918366	20040816

PRIORITY APPLN. INFO.:

US 1994-286521	A	19940805
US 1995-437841	B1	19950509
US 1995-438184	B1	19950509
WO 1995-US9464	W	19950725
US 1997-943682	A1	19971014
US 2000-741106	A1	20001221

AB Chimeric proteins possessing Kunitz-type domain 1 of TFPI-2 and Kunitz-type domain 2 of TFPI are provided, as are muteins of TFPI and TFPI-2. Nucleic acid sequences, expression vectors, and transformed host cells encoding and capable of producing the disclosed chimeric proteins and muteins are also provided. Chimeric proteins were constructed with amino acid sequences capable of binding a cell surface component (glycosaminoglycan, heparin) such as peptide moieties from protease nexin-1, protease nexin-2, antithrombin III, heparin cofactor II, protein C inhibitor, platelet factor 4, bovine pancreatic trypsin inhibitor, and ghilanten-related inhibitors. The chimeric proteins are produced as yeast  $\alpha$ -factor fusion proteins for secretion, or alternatively, may be expressed as a ubiquitin fusion protein. Potential sites for N-linked glycosylation within TFPI (Asn116→Gln, Asn227→Gln) are removed using overlapping PCR and mutations och1, mn1, and alg3 are introduced in transformed yeast cells to prevent the production of  $\alpha$ -1,6-polymannose terminal

carbohydrate moieties in the chimeric products. Finally, methods for prevention and treatment of septic shock using the chimeric proteins and muteins are described.

L6 ANSWER 46 OF 65 MEDLINE on STN  
ACCESSION NUMBER: 97115367 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 8956768  
TITLE: Prevention of endotoxin-induced mortality by antitissue factor immunization.  
AUTHOR: Dackiw A P; McGilvray I D; Woodside M; Nathens A B; Marshall J C; Rotstein O D  
CORPORATE SOURCE: Department of Surgery, Toronto Hospital, University of Toronto, Ontario.  
SOURCE: Archives of surgery (Chicago, Ill. : 1960), (1996 Dec) Vol. 131, No. 12, pp. 1273-8; discussion 1278-9. Journal code: 9716528. ISSN: 0004-0010.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199701  
ENTRY DATE: Entered STN: 28 Jan 1997  
Last Updated on STN: 28 Jan 1997  
Entered Medline: 14 Jan 1997

AB BACKGROUND: Microvascular thrombosis with intravascular fibrin deposition is a characteristic pathologic alteration during endotoxic shock. This effect is predominantly mediated by expression of the cellular procoagulant tissue factor by endothelial cells and cells of monocyte or macrophage lineage, resulting in acceleration of the coagulation cascade and fibrin deposition. OBJECTIVE: To determine whether modulation of this response by treatment with an antitissue factor antibody might have beneficial effects. DESIGN: A polyclonal antibody to murine tissue factor was prepared by injecting rabbits with a synthesized peptide sequence of murine tissue factor. To determine the activity of the antibody, elicited murine peritoneal macrophages were treated for 4 hours with 10-micrograms/mL lipopolysaccharide (LPS), and procoagulant activity was determined via a clotting assay (milliunits of activity per 10(6) macrophages). RESULTS: The tissue factor antibody abrogated LPS-induced macrophage procoagulant activity, confirming activity of the antibody (macrophages, 236 +/- 28 mU/10(6) macrophages; macrophages/LPS, 3801 +/- 190\* mU/10(6) macrophages; macrophages/LPS/alpha-tissue factor, 753 +/- 92\* mU/10(6) macrophages; n = 3; the asterisk indicates P < .05 by an analysis of variance). Additionally, antibody-protein affinity was confirmed by Western blot analysis. Having determined the activity of the antibody in vitro, we tested its efficacy in vivo in a lethal endotoxemia model. Mice were immunized with 200 microL of antiserum intraperitoneally 2 hours before injection with 250 micrograms of LPS intraperitoneally and 24 hours later. Control animals received 200 microL of saline solution. All animals initially exhibited lethargy and piloerection, characteristic of the predicted response to LPS. However, immunized animals had a significantly (P < .05) reduced mortality compared with control animals. Fibrinogen levels were significantly (P < .05) higher in the immunized mice, suggesting decreased consumption of coagulation factors, a finding consistent with an antitissue factor effect. Further, plasma tumor necrosis factor levels 90 minutes after LPS injection were similar in both groups, suggesting normal induction of the cytokine cascade. CONCLUSIONS: Modulation of microvascular fibrin deposition by abrogating tissue factor-mediated coagulation significantly (P < .05) improved survival in this model without attenuating the initiation of the cytokine cascade. These findings suggest a pathogenic role for coagulation in the induction of acute organ injury during sepsis.

L6 ANSWER 47 OF 65 MEDLINE on STN DUPLICATE 6  
 ACCESSION NUMBER: 97108219 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8950833  
 TITLE: In vitro expression and inhibition of procoagulant activity produced by bovine alveolar macrophages and peripheral blood cells.  
 AUTHOR: Rashid J; Weiss D J; Maheswaran S K; Murtaugh M P  
 CORPORATE SOURCE: Department of Veterinary Pathobiology, University of Minnesota, St Paul 55108, USA.  
 SOURCE: Veterinary research communications, (1996) Vol. 20, No. 6, pp. 519-31.  
 Journal code: 8100520. ISSN: 0165-7380.  
 PUB. COUNTRY: Netherlands  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199703  
 ENTRY DATE: Entered STN: 27 Mar 1997  
 Last Updated on STN: 27 Mar 1997  
 Entered Medline: 17 Mar 1997

AB Local and systemic activation of coagulation is frequently associated with bacterial sepsis. The coagulopathy is due, at least in part, to expression of tissue factor (TF) by monocytes and macrophages. The purpose of this study was to evaluate the expression of procoagulant activity by bovine alveolar macrophages, leukocytes and platelets, and to determine the relative potency of three chemical inhibitors of TF expression (pentoxifylline, retinoic acid, and cyclosporin A). Bovine alveolar macrophages were stimulated with lipopolysaccharide (LPS) derived from *Pasteurella haemolytica* or recombinant bovine tumour necrosis factor (TNF) and dose- and time-dependent effects on TF expression were studied. LPS and TNF induced TF expression in alveolar macrophages and LPS treatment of whole blood induced TF expression in mononuclear cells. Neutrophils and platelets also expressed procoagulant activity, but this activity was not inhibited by anti-bovine TF monoclonal antibody. Pentoxifylline (40  $\mu$ mol/L), retinoic acid (0.01 mmol/L) and cyclosporin A (0.08  $\mu$ mol/L) inhibited TF expression when added concurrently with LPS or TNF, but not when added 4 h after stimulation. TF mRNA was not detected in unstimulated alveolar macrophages by Northern blot analysis. In contrast, exposure to LPS or TNF for 6 h induced marked expression of TF mRNA, which was inhibited by treatment with pentoxifylline, retinoic acid and cyclosporin A. Expression of TNF by alveolar macrophages stimulated with LPS was also inhibited by these compounds. Our results indicate that procoagulant activity expressed by alveolar macrophages and monocytes is associated with expression of TF, whereas procoagulant activity expressed by neutrophils and platelets is not. The concentrations of pentoxifylline and retinoic acid necessary for inhibition of TF expression in vitro may not be achievable in vivo owing to their toxic effects. However, the in vitro concentration of cyclosporin A that inhibited TF expression did not exceed the plasma concentration observed in humans, and therefore may be useful for inhibition of TF expression in vivo.

L6 ANSWER 48 OF 65 MEDLINE on STN  
 ACCESSION NUMBER: 96283048 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8721387  
 TITLE: Comparison of the capacity of rhTNF-alpha and *Escherichia coli* to induce procoagulant activity by baboon mononuclear cells in vivo and in vitro.  
 AUTHOR: Li A; Chang A C; Peer G T; Hinshaw L B; Taylor F B Jr  
 CORPORATE SOURCE: Cardiovascular Biology Program, Oklahoma Medical Research Foundation, Oklahoma City 73104, USA.  
 SOURCE: Shock (Augusta, Ga.), (1996 Apr) Vol. 5, No. 4, pp. 274-9.  
 Journal code: 9421564. ISSN: 1073-2322.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199611  
ENTRY DATE: Entered STN: 19 Dec 1996  
Last Updated on STN: 19 Dec 1996  
Entered Medline: 7 Nov 1996

AB The procoagulant activity of mononuclear cells (MNCs) may play an important role in the disseminated intravascular coagulation seen in **septic shock**. This study compares the capacity of *Escherichia coli* (*E. coli*) and recombinant human TNF-alpha (rhTNF-alpha) to induce procoagulant activity by baboon MNCs. In vivo studies showed that MNC procoagulant activity was significantly increased at T + 120 min after LD100 *E. coli* infusion into baboons. Most of this procoagulant activity was attributable to **tissue factor**. In contrast, a bolus infusion of rhTNF-alpha (150 micrograms/kg) and a **monoclonal antibody** to activated protein C (2 mg/kg) did not induce any increase of MNC procoagulant activity at T + 120 min even though the plasma TNF-alpha level was 10 times higher than that seen following infusion of *E. coli*. In vitro studies showed that *E. coli* at concentrations comparable to that observed in the vivo study and LPS at a concentration of 2.5 ng/mL induced more intense **tissue factor** expression by both human and baboon monocytes than rhTNF-alpha in the concentrations ranging from 10 to 1,000 ng/mL. These results suggest that TNF-alpha alone is not sufficient to induced noticeable MNC procoagulant activity, at least, in the early stage of this **septic shock** model.

L6 ANSWER 49 OF 65 MEDLINE on STN  
ACCESSION NUMBER: 96136100 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 8547149  
TITLE: Induction of **tissue factor** expression  
in human monocyte/endothelium cocultures.  
AUTHOR: Collins P W; Noble K E; Reittie J R; Hoffbrand A V; Pasi K J; Yong K L  
CORPORATE SOURCE: Academic Department of Haematology, Royal Free Hospital and School of Medicine, London.  
SOURCE: British journal of haematology, (1995 Dec) Vol. 91, No. 4, pp. 963-70.  
Journal code: 0372544. ISSN: 0007-1048.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199602  
ENTRY DATE: Entered STN: 6 Mar 1996  
Last Updated on STN: 27 Mar 1996  
Entered Medline: 20 Feb 1996

AB Induction of **tissue factor** (TF) expression on monocytes and endothelial cells is central to the development of septic coagulopathy. Serum concentrations of endotoxin in septic patients who develop disseminated intravascular coagulation (DIC) do not, however, reach the levels that would directly stimulate TF expression on either monocytes or endothelium. We show, using an in vitro coculture system, that the interaction of monocytes with endothelium induces the expression of significant levels of TF. Unstimulated cocultures of monocytes (2 x 10<sup>4</sup>/well) and endothelial cells (2 x 10<sup>4</sup>/well) produced 35.3 +/- 8.5 mU of PCA/well, representing a 5-fold increase over the combined PCA of each cell type cultured alone (7.1 +/- 1.5 mU, n = 6, P < 0.001). Significant enhancement was also found in the presence of low concentrations of LPS. Induction of TF protein was confirmed by Western blotting. Fixation of monocytes with paraformaldehyde completely abolished TF induction in cocultures, whereas fixation of endothelium had

no effect, suggesting that TF induction occurred in monocytes rather than endothelial cells. Induction of TF in cocultures could be further augmented by preincubating the endothelial cells with IFN-gamma. When endothelium was prestimulated with 500 U/ml IFN-gamma there was 142 +/- 11% increase over unstimulated cocultures (n = 5, P < 0.01). TF induction was inhibited by 32 +/- 6% in the presence of anti-ICAM-1 mAb (n = 5, P < 0.01). Our results suggest that monocyte interactions with vascular endothelium, regulated by inflammatory cytokines, and mediated by adhesive ligand binding, leads to the induction of functional monocyte TF protein, which may be responsible for the initiation of DIC in sepsis.

=> dis ibib abs 30-39

YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' - CONTINUE?  
(Y)/N:y

L6 ANSWER 30 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2002:315102 CAPLUS  
DOCUMENT NUMBER: 136:337039  
TITLE: Tissue factor pathway inhibitor  
Ixolaris from Ixodes scapularis  
INVENTOR(S): Francischetti, Ivo M. B.; Valenzuela, Jesus G.;  
Ribeiro, Jose M.  
PATENT ASSIGNEE(S): The Government of the United States of America, as  
Represented by the Secretary, Department of Health and  
Human Services, USA  
SOURCE: PCT Int. Appl., 213 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002033089	A2	20020425	WO 2001-US42472	20011005
WO 2002033089	A3	20040226		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002030390	A5	20020429	AU 2002-30390	20011005
US 2004018516	A1	20040129	US 2003-408166	20030404
PRIORITY APPLN. INFO.:			US 2000-240575P	P 20001005
			WO 2001-US42472	W 20011005

AB Ixolaris, a novel protein with anticoagulant activity is described. Ixolaris can be isolated from the salivary glands of ticks or made by recombinant methods using various DNA expression techniques. Following sequencing of an I. scapularis salivary gland cDNA library, a clone with sequence homol. to tissue factor pathway inhibitor (TFPI) was identified. This cDNA codes for a mature protein, called Ixolaris, with 140 amino acids containing 10 cysteines and two Kunitz-like domains. Recombinant Ixolaris inhibits Factor VIIa(FVIIA)-induced Factor X activation with an IC50 in the pM range. Ixolaris behaves as a fast-and tight ligand of FXa and des-Gla-FXa (γ-carboxyglutamic acid domainless FXa), increasing their esterolytic activity .apprx.2-fold.

Ixolaris block the amidolytic activity of FVIIa/TF only in the presence of DEGR-FX or DEGR-FXa, but not des-Gla-DEGR-FXa. This result indicates that both FXa and FX are scaffolds for Ixolaris and implies that Gla-domain is necessary for Ixolaris/FX(a)/FVIIa/TF complex formation. Addnl., Ixolaris inhibits FIX activation by FVIIa/TF (Factor VIIa exosite inhibitor), and remarkable inhibition was achieved in the presence of FX/FXa. Western blotting using antibodies to Factor X and Factor VIIa shows that Ixolaris shifts the migration pattern of both Factor X and Factor Xa, but not Factor VIIa. Ixolaris is envisioned as being useful as an alternative anticoagulant in cardiovascular diseases as well as a vaccine target to prevent Lyme disease.

L6 ANSWER 31 OF 65 MEDLINE on STN DUPLICATE 3  
 ACCESSION NUMBER: 2002187052 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11918516  
 TITLE: New and emerging therapies for sepsis.  
 AUTHOR: Healy Daniel P  
 CORPORATE SOURCE: College of Pharmacy, University of Cincinnati, and Shriners Hospitals for Children, PO Box 670004, Cincinnati, OH 45267-0004, USA.. daniel.healy@uc.edu  
 SOURCE: The Annals of pharmacotherapy, (2002 Apr) Vol. 36, No. 4, pp. 648-54. Ref: 34  
 Journal code: 9203131. ISSN: 1060-0280.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200207  
 ENTRY DATE: Entered STN: 3 Apr 2002  
 Last Updated on STN: 25 Jul 2002  
 Entered Medline: 24 Jul 2002

AB OBJECTIVE: To review the recent advances related to the pathophysiology of sepsis and the rationale for recombinant human-activated protein C (drotrecogin alfa) and other antiseptis agents currently in Phase III trials. DATA SOURCES: A MEDLINE (1990-December 2001) search was performed to identify pertinent literature on the pathophysiology of sepsis and treatment strategies. The search was supplemented with AdisInsight (Adis International) using the search terms sepsis, severe sepsis, or septic shock combined with agents in Phase II or higher clinical development. Abstracts presented at infectious diseases and critical care meetings were also reviewed. STUDY SELECTION AND DATA EXTRACTION: Clinical efficacy studies were selected for drotrecogin alfa and other Phase III investigational agents. DATA SYNTHESIS: Our current understanding of the pathophysiology of sepsis underscores the contribution of increased coagulation and diminished fibrinolytic activity working in conjunction with an excessive and dysregulated inflammatory response. The loss of homeostatic balance among these systems results in a systemic inflammatory response with generalized coagulopathy, microvascular thrombosis, and, ultimately, acute organ failure and death. As a result of these advances, several compounds are now in various phases of development. A recombinant human form of endogenous activated protein C (drotrecogin alfa) was recently approved by the Food and Drug Administration for severe sepsis in adults who have a high risk of death. It possesses anticoagulant, profibrinolytic, and antiinflammatory properties. Other compounds currently in Phase III trials include tissue-factor pathway inhibitor, tumor-necrosis factor antibody fragment, platelet-activating factor acetylhydrolase, antithrombin III, and pyridoxylated hemoglobin polyoxyethylene. CONCLUSIONS: With the recent approval of drotrecogin alfa, there is renewed optimism that we can effectively reduce sepsis-associated mortality.

L6 ANSWER 32 OF 65 MEDLINE on STN



ACCESSION NUMBER: 2002464222 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 12223078  
 TITLE: **Tissue factor** - a therapeutic target  
 for thrombotic disorders.  
 AUTHOR: Houston Donald S  
 CORPORATE SOURCE: Section of Hematology/Oncology, Department of Internal  
 Medicine, University of Manitoba, 675 McDermot Avenue,  
 Winnipeg, Manitoba, R3E 0V9, Canada..  
 houston@cc.umanitoba.ca  
 SOURCE: Expert opinion on therapeutic targets, (2002 Apr) Vol. 6,  
 No. 2, pp. 159-74. Ref: 154  
 Journal code: 101127833. E-ISSN: 1744-7631.  
 PUB. COUNTRY: England: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200509  
 ENTRY DATE: Entered STN: 12 Sep 2002  
 Last Updated on STN: 13 Dec 2002  
 Entered Medline: 12 Sep 2005  
 AB Exposure of blood to **tissue factor** (TF) sets off the  
 coagulation cascade. TF is a transmembrane protein that serves as an  
 essential cofactor for activated coagulation factor VII (FVIIa). TF may  
 be exposed locally by vascular injury (such as balloon angioplasty) or by  
 spontaneous rupture of an atherosclerotic plaque. Expression of TF may  
 also be induced on monocytes and endothelial cells in conditions like  
**sepsis** and cancer, causing a more generalised activation of  
 clotting. TF may thus play a central role in thrombosis in a number of  
 settings, and attention has turned to blocking TF as a means to prevent  
 thrombosis. Inhibiting the inducible expression of TF by monocytes can be  
 achieved by 'deactivating' cytokines, such as interleukin (IL)-4, -10 and  
 -13, or by certain prostanoids; by drugs that modify signal transduction,  
 such as pentoxifylline, retinoic acid or vitamin D(3), or by antisense  
 oligonucleotides. Such approaches are for the most part at a preclinical  
 stage. The function of TF can be blocked by **antibodies** that  
 prevent the binding of FVIIa to TF; by active site-inhibited FVIIa, which  
 competes with native FVIIa for binding; by **antibodies** or small  
 molecules that block the function of the TF/FVIIa complex; and by  
 molecules, such as TF pathway inhibitor or nematode anticoagulant peptide  
 C2, which inhibit the active site of FVIIa in the TF/FVIIa complex after  
 first binding to activated factor X. The latter two agents have entered  
 Phase II clinical trials. Perhaps most intriguing is the use of anti-TF  
 agents locally, which holds the promise of stopping thrombosis at a  
 specific site of injury without the bleeding risk associated with systemic  
 anticoagulation.

L6 ANSWER 33 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights  
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ACCESSION NUMBER: 2002253993 EMBASE  
 TITLE: Pharmacology of acute lung injury.  
 AUTHOR: Tasaka S.; Hasegawa N.; Ishizaka A.  
 CORPORATE SOURCE: Dr. A. Ishizaka, Department of Laboratory Medicine, Tokyo  
 Electric Power Company Hosp., 9-2 Shinanomachi,  
 Shinjuku-ku, Tokyo 160-0016, Japan. ishiz@attglobal.net  
 SOURCE: Pulmonary Pharmacology and Therapeutics, (2002) Vol. 15,  
 No. 2, pp. 83-95. .  
 Refs: 150  
 ISSN: 1094-5539 CODEN: PPTHFJ  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
 015 Chest Diseases, Thoracic Surgery and Tuberculosis  
 025 Hematology

030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 25 Jul 2002  
Last Updated on STN: 25 Jul 2002

AB The acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is a clinical syndrome that affects both medical and surgical patients. To date, despite improved understanding of the pathogenesis of ALI/ARDS, pharmacological modalities have been unsuccessful in decreasing mortality. However, several pharmacological agents for ARDS are in development and have shown great promise. In addition to the anti-inflammatory category including late corticosteroids, inhaled nitric oxide, alveolar surfactant, and vasodilators are being evaluated. Replacements of anticoagulation mediators have also suggested beneficial effects on the patient outcome. This article provides an overview of pharmacological treatments of ALI/ARDS. .COPYRGT. 2002 Elsevier Science Ltd. All rights reserved.

L6 ANSWER 34 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:713567 CAPLUS  
DOCUMENT NUMBER: 135:271900  
TITLE: Anti-tissue factor  
antibodies with enhanced anticoagulant potency  
INVENTOR(S): Kirchhofer, Daniel K.; Lowe, David G.; Presta, Leonard G.  
PATENT ASSIGNEE(S): Genentech, Inc., USA  
SOURCE: PCT Int. Appl., 75 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070984	A2	20010927	WO 2001-US7501	20010308
WO 2001070984	A3	20020228		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2402596	AA	20010927	CA 2001-2402596	20010308
EP 1263960	A2	20021211	EP 2001-924131	20010308
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2003527861	T2	20030924	JP 2001-569367	20010308
PRIORITY APPLN. INFO.:			US 2000-189775P	P 20000316
			WO 2001-US7501	W 20010308

AB The invention concerns anti-tissue factor (anti-TF) antibodies with enhanced anticoagulant potency, and methods and means for identifying, producing and using such antibodies. The anti-TF antibodies of the present invention are designed to comprise a region binding to an epitope in the C-terminal macromol. substrate binding region of TF. The macromol. substrate is factor X or factor IX; the antibodies are monoclonal antibodies, humanized antibodies or human antibodies; and the disease is deep venous thrombosis, arterial thrombosis, stroke, tumor metastasis, arteriosclerosis, restenosis following angioplasty, acute and chronic inflammation, septic

shock, septicemia, hypotension, adult respiratory distress syndrome and disseminated intravascular coagulopathy.

L6 ANSWER 35 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001219534 EMBASE  
TITLE: Beneficial effect of glycoprotein IIb/IIIa inhibitor (AZ-1) on endothelium in Escherichia coli endotoxin-induced shock.  
AUTHOR: Pu Q.; Wiel E.; Corseaux D.; Bordet R.; Azrin M.A.; Ezekowitz M.D.; Lund N.; Jude B.; Vallet B.  
CORPORATE SOURCE: Dr. B. Vallet, Dept. d'Anesthesie-Reanimation 2, Hopital Claude Huriez, Ctr. Hosp. Universitaire de Lille, 59037 Lille, Cedex, France. bvallet@chru-lille.fr  
SOURCE: Critical Care Medicine, (2001) Vol. 29, No. 6, pp. 1181-1188. .  
Refs: 47  
ISSN: 0090-3493 CODEN: CCMDC7  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 004 Microbiology  
024 Anesthesiology  
025 Hematology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 10 Jul 2001  
Last Updated on STN: 10 Jul 2001

AB Objective: To investigate the effects of AZ-1, a murine monoclonal antiglycoprotein-IIb/IIIa antibody, on endothelium and on hemostasis in a rabbit endotoxic shock model. Design: Prospective laboratory study. Setting: University laboratory. Subjects: Thirty-five male New-Zealand rabbits. Interventions: In vitro vascular reactivity, endothelium CD31-PECAM1 immunohistochemistry, plasma coagulation factors, and monocyte tissue factor determination were performed 1 day and/or 5 days after onset of endotoxic shock (0.5 mg/kg, intravenous bolus, Escherichia coli lipopolysaccharide) with or without treatment by AZ-1 (0.5 mg/kg intravenously) given 1 hr after lipopolysaccharide injection. Measurements and Main Results: Metabolic acidosis and coagulation activation confirmed the presence of shock. AZ-1 treatment improved endothelial-dependent relaxation at 1 day (maximal effect =  $87.2 \pm 4.0\%$  vs.  $60.9 \pm 5.2\%$  in the nontreated group,  $p < .05$ ) and at 5 days (maximal effect =  $84.5 \pm 3.5\%$  vs.  $56.6 \pm 8.2\%$  in the nontreated group,  $p < .05$ ). Endotoxin-induced endothelial injury was decreased significantly by AZ-1 at 1 day ( $6.4 \pm 1.9\%$  vs.  $10.3 \pm 0.8\%$  in the nontreated group,  $p < .05$ ) and at 5 days ( $6.3 \pm 2.0\%$  vs.  $20.2 \pm 1.2\%$  in the nontreated group,  $p < .05$ ). Monocyte tissue factor expression was significantly reduced at 5 days. Conclusions: These data indicate that potent inhibition of platelet function via antiglycoprotein-IIb/IIIa receptor blockade can inhibit coagulation activation and protect against endothelial dysfunction and histologic injury in endotoxin-induced shock.

L6 ANSWER 36 OF 65 MEDLINE on STN DUPLICATE 4  
ACCESSION NUMBER: 2002010417 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11372673  
TITLE: Microparticles from patients with multiple organ dysfunction syndrome and sepsis support coagulation through multiple mechanisms.  
AUTHOR: Joop K; Berckmans R J; Nieuwland R; Berkhout J; Romijn F P; Hack C E; Sturk A  
CORPORATE SOURCE: Department of Clinical Chemistry, Leiden University Medical Center, The Netherlands.  
SOURCE: Thrombosis and haemostasis, (2001 May) Vol. 85, No. 5, pp. 810-20.

Journal code: 7608063. ISSN: 0340-6245.  
PUB. COUNTRY: Germany: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200202  
ENTRY DATE: Entered STN: 21 Jan 2002  
Last Updated on STN: 20 Feb 2002  
Entered Medline: 19 Feb 2002

AB AIM: We investigated the occurrence and thrombin generating mechanisms of circulating microparticles (MP) in patients with multiple organ dysfunction syndrome (MODS) and sepsis. METHODS: MP, isolated from blood of patients (n = 9) and healthy controls (n = 14), were stained with cell-specific monoclonal antibodies (MoAbs) or anti-tissue factor (anti-TF) MoAb and annexin V, and analyzed by flow cytometry. To assess their thrombin-generating capacity, MP were reconstituted in normal plasma. The coagulation activation status in vivo was quantified by plasma prothrombin fragment F1+2- and thrombin-antithrombin (TAT) measurements. RESULTS: Annexin V-positive MP in the patients originated predominantly from platelets (PMP), and to a lesser extent from erythrocytes, endothelial cells (EMP) and granulocytes (GMP). Compared to healthy controls, the numbers of annexin V-positive PMP and TF-exposing MP were decreased (p = <0.001 for both), EMP were decreased (E-selectin, p = 0.003) or found equal (CD144, p = 0.063), erythrocyte-derived MP were equal (p = 0.726), and GMP were increased (p = 0.008). GMP numbers correlated with plasma concentrations of elastase (r = 0.70, p = 0.036), but not with C-reactive-protein or interleukin-6 concentrations. Patient samples also contained reduced numbers of annexin V-negative PMP, and increased numbers of erythrocyte-derived MP and GMP (p = 0.005, p = 0.021 and p <0.001, respectively). Patient MP triggered thrombin formation, which was reduced compared to the healthy controls (p = 0.008) and strongly inhibited by an anti-factor XII MoAb (two patients), by anti-factor XI MoAb (eight patients) or by anti-TF MoAb (four patients). Concentrations of F1+2 and TAT were elevated (p = 0.005 and p = 0.001, respectively) and correlated inversely with the number of circulating MP (and r = -0.51, p = 0.013, and r = -0.65, p = 0.001, respectively) and their thrombin generation capacity (F1+2: r = -0.62, p = 0.013). CONCLUSIONS: In patients with MODS and sepsis relatively low numbers of MP are present that differ from controls in their cellular origin, numbers and coagulation activation mechanisms.

L6 ANSWER 37 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:198900 BIOSIS  
DOCUMENT NUMBER: PREV200200198900  
TITLE: Factor VIIa-antithrombin complexes in plasma.  
AUTHOR(S): Morrissey, James H. [Reprint author]; Bianco-Fisher, Emma; Parizi-Robinson, Mojgan  
CORPORATE SOURCE: Biochemistry, University of Illinois, Urbana, IL, USA  
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 526a. print.  
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.  
CODEN: BLOOAW. ISSN: 0006-4971.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
Conference; (Meeting Poster)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20 Mar 2002  
Last Updated on STN: 20 Mar 2002

AB Coagulation factor VIIa, the first enzyme in the clotting cascade, is unreactive with plasma protease inhibitors when in solution and circulates with a relatively long 2 hr half-life even in the activated state. We

previously showed that about 1% of total factor VII circulates as factor VIIa (the active enzyme), with considerable variation from person to person. On the other hand, when factor VIIa binds to tissue factor (its essential protein cofactor), it acquires full proteolytic activity and also full reactivity with plasma protease inhibitors such as tissue factor pathway inhibitor (TFPI) and antithrombin (formerly antithrombin III). In the latter case, this results in the formation of covalent factor VIIa-antithrombin complexes (VIIa-AT). Interestingly, VIIa-AT complexes lose affinity for tissue factor and thus should be released back into the plasma. We therefore hypothesized that plasma levels of VIIa-AT should reflect the degree of intravascular tissue factor exposure, and so may be a marker of underlying inflammatory states that could predispose to thrombotic events. To test this hypothesis, we developed a two-antibody ELISA that is specific and sensitive for VIIa-AT. The ELISA captures VIIa-AT complexes using an immobilized, calcium-independent monoclonal antibody against factor VII/VIIa (whose epitope is not obscured by antithrombin), and it detects the complexes using an antibody specific for antithrombin. It is capable of measuring trace levels of VIIa-AT present in plasma, with a lower limit of detection of about 2 pM. All normal individuals so far examined had readily measurable VIIa-AT levels. These levels were surprisingly high (ranging from 50 to 300 pM VIIa-AT, or roughly 1.5% of the total factor VII plasma), suggesting that antithrombin is a major regulator of basal factor VIIa levels in vivo. This finding is surprising as it was previously thought that TFPI was more important than antithrombin in regulating factor VIIa activity in vivo. Plasma VIIa-AT levels were only weakly correlated with plasma factor VIIa levels and were found to change markedly during sepsis or in response to heparin.

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ACCESSION NUMBER: 2001112156 EMBASE  
 TITLE: Tissue factor as a therapeutic target.  
 AUTHOR: Key N.S.; Bach R.R.  
 CORPORATE SOURCE: Dr. N.S. Key, Div. of Hematol. Oncol./Transplant.,  
 University of Minnesota, Medical School, Minneapolis, MN  
 55455, United States. keyxx001@tc.umn.edu  
 SOURCE: Thrombosis and Haemostasis, (2001) Vol. 85, No. 3, pp.  
 375-376. .  
 Refs: 10  
 ISSN: 0340-6245 CODEN: THHADQ  
 COUNTRY: Germany  
 DOCUMENT TYPE: Journal; Note  
 FILE SEGMENT: 025 Hematology  
 018 Cardiovascular Diseases and Cardiovascular Surgery  
 037 Drug Literature Index  
 030 Pharmacology  
 005 General Pathology and Pathological Anatomy  
 029 Clinical Biochemistry  
 016 Cancer  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 12 Apr 2001  
 Last Updated on STN: 12 Apr 2001

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L6 ANSWER 39 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002054649 EMBASE  
 TITLE: Regulation of inflammatory responses by natural  
 anticoagulants.  
 AUTHOR: Okajima K.  
 CORPORATE SOURCE: K. Okajima, Department of Laboratory Medicine, Kumamoto

Univ. School of Medicine, Honjo 1-1-1, Kumamoto 860-0811,  
Japan. whynot@kaiju.medic.kumamoto-u.ac.jp  
SOURCE: Immunological Reviews, (2001) Vol. 184, pp. 258-274. .  
Refs: 153  
ISSN: 0105-2896 CODEN: IMRED2  
COUNTRY: Denmark  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 025 Hematology  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 21 Feb 2002  
Last Updated on STN: 21 Feb 2002

AB Proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are critically involved in activation of the coagulation system in sepsis, leading to disseminated intravascular coagulation (DIC). Natural anticoagulants such as antithrombin (AT) and activated protein C (APC) regulate the coagulation system by inhibiting thrombin generation. In addition to these anticoagulant effects, both AT and APC have been shown to attenuate inflammatory responses induced by various noxious stimuli in rats such as lipopolysaccharide (LPS) challenge. AT promotes the endothelial release of prostacyclin, a potent anti-inflammatory prostaglandin that inhibits the monocytic production of TNF- $\alpha$ , by interacting with cell-surface heparin-like substances. APC directly inhibits the production of TNF- $\alpha$  by inhibiting the activation of both nuclear factor  $\kappa$ B (NF $\kappa$ B) and activator protein-1 in monocytes stimulated with LPS. Thrombomodulin, an endothelial membranous integral protein that binds thrombin, exerts anti-inflammatory effects by generating APC. Furthermore, tissue factor pathway inhibitor, a natural anticoagulant for the extrinsic pathway of the coagulation system, also attenuates LPS-induced inflammatory responses in rats by inhibiting TNF- $\alpha$  production by monocytes. These findings strongly suggest that natural anticoagulants could regulate inflammatory responses as well as the coagulation system in rats by inhibiting the monocytic production of TNF- $\alpha$ . Such anti-inflammatory properties of natural anticoagulants are potentially important for their replacement in patients with sepsis who frequently develop DIC and organ failure as inflammatory responses.

=> dis ibib abs 20-29

YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' - CONTINUE?  
(Y)/N:y

L6 ANSWER 20 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004045843 EMBASE  
TITLE: Mediator modulation therapy of severe sepsis and septic shock: Does it work?.  
AUTHOR: Dellinger R.P.; Parrillo J.E.  
CORPORATE SOURCE: Dr. R.P. Dellinger, Department of Medicine, Univ. Med. and Dent. of New Jersey, Cooper University Hospital, Camden, NJ, United States  
SOURCE: Critical Care Medicine, (2004) Vol. 32, No. 1, pp. 282-286.  
Refs: 49  
ISSN: 0090-3493 CODEN: CCMDC7  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Editorial  
FILE SEGMENT: 004 Microbiology  
005 General Pathology and Pathological Anatomy

025 Hematology  
037 Drug Literature Index  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20 Feb 2004  
Last Updated on STN: 20 Feb 2004

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L6 ANSWER 21 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:892884 CAPLUS  
DOCUMENT NUMBER: 139:380016  
TITLE: Novel **tissue factor** targeted  
**antibodies** as anticoagulants  
INVENTOR(S): Light, David; McLean, Kirk  
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany  
SOURCE: PCT Int. Appl., 58 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093422	A2	20031113	WO 2003-US13521	20030430
WO 2003093422	A3	20040715		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2483910	AA	20031113	CA 2003-2483910	20030430
US 2004063632	A1	20040401	US 2003-427805	20030430
BR 2003004660	A	20050607	BR 2003-4660	20030430
EP 1549341	A2	20050706	EP 2003-721974	20030430
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
CN 1665526	A	20050907	CN 2003-815702	20030430
CN 1665534	A	20050907	CN 2003-815703	20030430
JP 2005532045	T2	20051027	JP 2004-501558	20030430
NO 2003005848	A	20040227	NO 2003-5848	20031230
PRIORITY APPLN. INFO.:			US 2002-376566P	P 20020501
			WO 2003-US13521	W 20030430

AB This invention relates to novel **antibodies** that bind with greater affinity to the factor VIIa/**tissue factor** (FVIIa/TF) complex than to **tissue factor** (TF) alone, do not compete for binding to TF with FVII and FX, and inhibit FX activation. The **antibodies** bind at the site of injury and prevent the initiation of thrombosis. The **antibodies** can be used to treat a variety of thrombotic conditions including but not limited to deep vein thrombosis, disseminated intravascular coagulation, and acute coronary syndrome.

L6 ANSWER 22 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:892550 CAPLUS  
DOCUMENT NUMBER: 139:376205  
TITLE: **Tissue factor** targeted  
**antibody**-thrombomodulin fusion proteins as  
anticoagulants  
INVENTOR(S): Light, David; McLean, Kirk

PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany  
 SOURCE: PCT Int. Appl., 67 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003092602	A2	20031113	WO 2003-US13522	20030430
WO 2003092602	A3	20040826		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2483909	AA	20031113	CA 2003-2483909	20030430
US 2004063632	A1	20040401	US 2003-427805	20030430
BR 2003004659	A	20040921	BR 2003-4659	20030430
EP 1503785	A2	20050209	EP 2003-721975	20030430
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1665526	A	20050907	CN 2003-815702	20030430
CN 1665534	A	20050907	CN 2003-815703	20030430
JP 2005538046	T2	20051215	JP 2004-500787	20030430
NO 2003005849	A	20040227	NO 2003-5849	20031230
PRIORITY APPLN. INFO.:			US 2002-376566P	P 20020501
			WO 2003-US13522	W 20030430

AB The present invention provides novel fusion proteins, which act as anticoagulants, and comprise a targeting protein, that interacts with either tissue factor (TF) or the factor VIIa/tissue factor ("FVIIa/TF") complex, which is operably linked to the thrombomodulin (TM) EGF456 domain alone or in combination with at least one other domain selected from the group consisting of the N-terminal hydrophobic region domain, the EGF123 domain, the interdomain loop between EGF3 and EGF4, and the O-glycosylated Ser/Thr-rich domain, or analogs, fragments, derivs. or variants thereof. The anticoagulant fusion protein of this invention targets and binds TF or the FVIIa/TF complex at the site of injury, localizing to the injury site, and thus preventing thrombus formation and thereby performing more effectively as an anticoagulant compared to either a soluble anti-TF antibody or soluble or fragments of. In another aspect, the invention relates to a method for preventing and treating deep vein thrombosis (DVT) or disseminated intravascular coagulation (DIC) or acute coronary syndrome or cancer with evidence of coagulopathy in a patient comprising administering a therapeutically effective amount of the fusion protein to said patient. The invention also relates to a method for regulating the inflammatory response in a patient comprising administering a therapeutically effective amount of the fusion protein to said patient. The fusion protein of the invention can be used to form a nonthrombogenic coating on the surface of medical devices contacting blood. Seven different TF-binding antibodies were isolated from a fully human single chain antibody phage display library. From among seven different antibodies isolated, only one of them, scFv(TF)3e10, did not inhibit the sTFNIIa assay. This antibody increased the affinity of FVIIa for sTF, decreasing the KD 5-fold. These expts. revealed that the antibody has a 20-fold higher affinity for the TF/FVIIa complex as compared to free sTF (33 nM vs. 600 nM). Although the



scFv(TF)3e10 antibody did not have the highest affinity as measured by BIAcore and it increased the affinity of FVIIa for sTF, it was the only antibody in the group that inhibited FX activation and prolonged the clotting time in the PT assay. The antibody binds to a unique epitope on human TF that interferes with activation of FX by the FVila/TF complex. The fusion protein, scFv(TF)3e10-TMi456, retained the ability of inhibit FX activation by the FVila/TF complex (IC50 = 0.5 nM, data not shown) and acted as a cofactor for the thrombin catalyzed activation of protein C (chromogenic assay) contrast, the cofactor activity of the fusion protein, but not TMi456, was enhanced >5-fold in the presence of TF-containing phospholipid vesicles. The in vitro potency of the fusion protein, scFv(TF)3e10-TMi456, against TF-induced coagulation (PT assay, extrinsic coagulation pathway) was 6-fold better than the scFv(TF)3e10 antibody and 17-fold better than TMi456 alone. In agreement with the plasma-based coagulation assays, the fusion protein scFv(TF)3e10-TMi456 was more potent in a TF-induced whole blood coagulation assay (Thromboelastograph, TEG) than either scFv(TF)3e10 or TMi456 alone. In summary, the above data demonstrate that the fusion proteins of the invention are potent and selective anticoagulants in vitro. The fusion protein of the invention was able to inhibit death and respiratory distress in rat model of disseminated intravascular coagulation (DIC).

L6 ANSWER 23 OF 65 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:532486 CAPLUS  
DOCUMENT NUMBER: 139:79186  
TITLE: Treatment of sepsis by low dose administration of tissue factor pathway inhibitor (TFPI)  
INVENTOR(S): Creasey, Alba A.  
PATENT ASSIGNEE(S): Chiron Corporation, USA  
SOURCE: PCT Int. Appl., 58 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055442	A2	20030710	WO 2002-US32625	20021015
WO 2003055442	A3	20040304		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2463738	AA	20030710	CA 2002-2463738	20021015
US 2003139339	A1	20030724	US 2002-270478	20021015
EP 1446138	A2	20040818	EP 2002-803284	20021015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013293	A	20041221	BR 2002-13293	20021015
CN 1604787	A	20050406	CN 2002-825064	20021015
JP 2005515214	T2	20050526	JP 2003-556020	20021015
US 2003139340	A1	20030724	US 2003-270479	20030204
ZA 2004003690	A	20050308	ZA 2004-3690	20040513
JP 2006008704	A2	20060112	JP 2005-271191	20050916
JP 2006008706	A2	20060112	JP 2005-271219	20050916

PRIORITY APPLN. INFO.:

US 2001-328806P	P 20011015
JP 2003-535710	A3 20021015
JP 2003-556020	A3 20021015
WO 2002-US32625	W 20021015

AB Methods for prophylactically or therapeutically treating **sepsis** or **septic shock** involve administration of **tissue factor pathway inhibitor (TFPI)** or a **TFPI analog** to patients suffering from **sepsis** or other inflammatory conditions. The methods involve the use of continuous i.v. infusion of **TFPI** or a **TFPI analog** at low doses to avoid adverse side effects. Low doses of recombinant Ala-TFPI were administered to septic human patients.

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ACCESSION NUMBER: 2003506984 EMBASE  
 TITLE: Pharmacologic treatment of acute renal failure in **sepsis**.  
 AUTHOR: De Vriese A.S.; Bourgeois M.  
 CORPORATE SOURCE: A.S. De Vriese, Renal Unit, AZ Sint-Jan AV, Ruddershove, 10, B-8000, Brugge, Belgium. an.devriese@azbrugge.be  
 SOURCE: Current Opinion in Critical Care, (2003) Vol. 9, No. 6, pp. 474-480. .  
 Refs: 78  
 ISSN: 1070-5295 CODEN: COCCF7  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 006 Internal Medicine  
 026 Immunology, Serology and Transplantation  
 028 Urology and Nephrology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 30 Dec 2003  
 Last Updated on STN: 30 Dec 2003

AB The pathophysiology of acute renal failure in **sepsis** is complex and includes intrarenal vasoconstriction, infiltration of inflammatory cells in the renal parenchyma, intraglomerular thrombosis, and obstruction of tubuli with necrotic cells and debris. Attempts to interfere pharmacologically with these dysfunctional pathways, including inhibition of inflammatory mediators, improvement of renal hemodynamics by amplifying vasodilator mechanisms and blocking vasoconstrictor mechanisms, and administration of growth factors to accelerate renal recovery, have yielded disappointing results in clinical trials. Interruption of leukocyte recruitment is a potential promising approach in the treatment of septic acute renal failure, but no data in humans are presently available. Activated protein C and steroid replacement therapy have been shown to reduce mortality in patients with **sepsis** and are now accepted adjunctive treatment options for **sepsis** in general.

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ACCESSION NUMBER: 2003339936 EMBASE  
 TITLE: Targeting **tissue factor** as an antithrombotic strategy.  
 AUTHOR: Golino P.; Cimmino G.  
 CORPORATE SOURCE: Dr. P. Golino, Division of Cardiology, Seconda Universita di Napoli, Piazza L. Miraglia, 80138 Naples, Italy  
 SOURCE: Seminars in Vascular Medicine, (2003) Vol. 3, No. 2, pp. 205-213. .  
 Refs: 83  
 ISSN: 1528-9648 CODEN: SVMECD  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
018 Cardiovascular Diseases and Cardiovascular Surgery  
025 Hematology  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 11 Sep 2003

Last Updated on STN: 11 Sep 2003

AB It is generally accepted that the initial event in coagulation and intravascular thrombus formation is the exposure of cell-surface protein, such as **tissue factor (TF)**. TF is exposed to the flowing blood as a consequence of vascular injury induced, for instance, by PTCA, or by spontaneous rupture of an atherosclerotic plaque. Expression of TF may also be induced in monocytes and endothelial cells in several conditions such as **sepsis** and cancer, causing a more generalized activation of clotting. In addition to its essential role in hemostasis, TF may be also implicated in several pathophysiological processes, such as intracellular signaling, cell proliferation, and inflammation. For all these reasons, TF has been the subject of intense research focus. Many experimental studies have demonstrated that inhibition of TF:factor VIIa procoagulant activity is a powerful inhibitor of in vivo thrombosis and that this approach usually results in a less-pronounced bleeding tendency compared with other "more classical" antithrombotic interventions. Alternative approaches may be represented by **antibodies** directed against TF, by transfection of the arterial wall with natural inhibitors of the TF:factor VIIa complex, such as the TF pathway inhibitor, or with catalytic RNA (ribozyme), which could inhibit the expression of the TF protein by the disruption of cellular TF mRNA. All these approaches seem particularly attractive because they may result in complete inhibition of local thrombosis without incurring potentially harmful systemic effects. Further studies are warranted to determine the efficacy and safety of such approaches in patients.

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ACCESSION NUMBER: 2003330254 EMBASE

TITLE: Surgical **sepsis**: Dysregulation of immune function and therapeutic implications.

AUTHOR: Boontham P.; Chandran P.; Rowlands B.; Eremin O.

CORPORATE SOURCE: P. Boontham, Department of Surgery, Queens Medical Centre, University of Nottingham, Nottingham NG7 2UH, United Kingdom

SOURCE: Surgeon, (2003) Vol. 1, No. 4, pp. 187-206. .  
Refs: 142

ISSN: 1479-666X CODEN: SURGB2

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology  
009 Surgery  
017 Public Health, Social Medicine and Epidemiology  
026 Immunology, Serology and Transplantation  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 28 Aug 2003

Last Updated on STN: 28 Aug 2003

AB **Sepsis** is defined clinically as the systemic inflammatory response of the host to the documented systemic infection. The pathophysiological disturbance involves both the innate and adaptive immune systems encompassing cellular immunity, humoral components and the complement system. Dendritic cells (antigen-presenting cells) are key cells involved in the regulation of the immune response in **sepsis**

, in particular in activating T cells and especially inducing the production and secretion of specific cytokines. These are the main mediators in establishing prominent disturbances of inflammation in patients with **sepsis**. The clinical features of the **sepsis** syndrome may vary from minor clinical disturbances to severe multiple organ failure and death of the host. Appropriate therapeutic strategies for patients with **sepsis** utilise conventional therapy and new novel forms of treatment, which are showing promise for the future.

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ACCESSION NUMBER: 2003166393 EMBASE  
TITLE: Update on **septic shock**: The latest approaches to treatment - How new treatment modalities may improve outcomes.  
AUTHOR: Cruz K.; Hollenberg S.  
CORPORATE SOURCE: Dr. K. Cruz, Northwest Community Healthcare, Arlington Heights, IL, United States  
SOURCE: Journal of Critical Illness, (1 Apr 2003) Vol. 18, No. 4, pp. 162-168. .  
Refs: 28  
ISSN: 1040-0257 CODEN: JCILFN  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 006 Internal Medicine  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 19 May 2003  
Last Updated on STN: 19 May 2003

AB Empiric antibiotic therapy covering gram-negative and gram-positive organisms should begin immediately for **septic shock**, because the causal pathogens are unknown in almost 40% to 50% of cases and data support improved outcomes when appropriate antibiotics are instituted early in the course of disease. The management strategy is 3-pronged: interrupt the septic cascade leading to shock; identify and eradicate the source of infection via antibiotic therapy and/or surgical drainage; and maintain adequate organ perfusion and function. Hemodynamic monitoring, volume resuscitation, and inotropic support to increase regional perfusion indices are the cornerstones of therapy. The judicious use of glucocorticoid replacement may improve outcome in selected patients. Newer therapies center around endogenous agents with restorative immunomodulating properties. The FDA approval of drotrecogin alfa (recombinant human activated protein C) heralds this new generation of agents. Recombinant **tissue factor** pathway inhibitors and **monoclonal antibodies** are also being investigated.

L6 ANSWER 28 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003241787 EMBASE  
TITLE: Identification of meningococcal LPS as a major monocyte activator in IL-10 depleted shock plasmas and CSF by blocking the CD14-TLR4 receptor complex.  
AUTHOR: Bjerre A.; Brusletto B.; Ovstebo R.; Joo G.B.; Kierulf P.; Brandtzaeg P.  
CORPORATE SOURCE: A. Bjerre, Department of Pediatrics, Ulleval University Hospital, 0407 Oslo, Norway. a.k.bjerre@ioks.uio.no  
SOURCE: Journal of Endotoxin Research, (2003) Vol. 9, No. 3, pp. 155-163. .  
Refs: 42  
ISSN: 0968-0519 CODEN: JENREB

COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 004 Microbiology  
025 Hematology  
052 Toxicology  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 3 Jul 2003  
Last Updated on STN: 3 Jul 2003

AB We have examined the in vitro stimulatory effects of lipopolysaccharide (LPS)-containing samples (meningococcal shock plasma, n = 10; non-shock plasma, n = 10; cerebrospinal fluid (CSF), n = 7) before and after immunodepletion of interleukin (IL)-10 in a monocyte target assay. We also studied the stimulatory effects of plasma collected from 3 patients with lethal septicemia caused by *Streptococcus pneumoniae* without detectable LPS but with 100-fold increased levels of heat-shock protein 70 (HSP70). HSP70 may, like LPS, activate monocytes via the Toll-like receptor 4 (TLR4). The samples were analyzed for LPS, tumor necrosis factor (TNF)- $\alpha$ , IL-10 and HSP70; applied on human monocytes (purity > 95%) before and after IL-10 immunodepletion, in the absence or presence of CD14 blocking mAb (60bca) or the lipid A antagonist, *Rhodobacter sphaeroides* diphosphoryl lipid A (RsDPLA) which blocks TLR4. Monocyte activation was measured by increased TNF- $\alpha$  secretion and tissue factor (TF) up-regulation by monocyte procoagulant activity (PCA). There was a positive correlation between patient plasma LPS levels (n = 10) and increases in TNF- $\alpha$  secretion by the monocytes after immunodepletion of IL-10 (r = 0.82). Pretreatment of the monocytes with mAbCD14 or RsDPLA reduced TNF- $\alpha$  secretion to median 5% and 12%, respectively, of the levels before the receptor complex was blocked. The median levels of HSP70 were 543 ng/ml (range, 468-962 ng/ml) in pneumococcal shock plasma, 81.5 ng/ml (range, 41-331 ng/ml) in meningococcal shock plasma and 24 ng/ml (range, < 0.8-41 ng/ml) in meningococcal non-shock plasma. Pneumococcal septic shock plasmas with significantly higher levels of HSP70 (P < 0.05) did not induce TNF- $\alpha$  secretion in the monocytes. The results strongly suggest that LPS in meningococcal shock plasma is the major activator of monocytes whereas HSP70 (in plasma concentrations up to 963 ng/ml) does not activate monocytes in this assay.

L6 ANSWER 29 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:238121 BIOSIS  
DOCUMENT NUMBER: PREV200400238371  
TITLE: A humanized anti-tissue factor monoclonal antibody (CNTO 859) inhibits procoagulant effects of LPS challenge in a cynomolgus monkey model.  
AUTHOR(S): Tam, S. H. [Reprint Author]; Picha, K. M. [Reprint Author]; Khandekar, V. S. [Reprint Author]; Soderman, A. R. [Reprint Author]; Martin, E. C.; Nedelman, M. A.; Bugelski, P. [Reprint Author]; Jordan, R. E. [Reprint Author]  
CORPORATE SOURCE: Centocor, Inc., 145 King of Prussia Rd., Radnor, PA, 19087, USA  
SOURCE: Inflammation Research, (July 2003) Vol. 52, No. Supplement 2, pp. S 136. print.  
Meeting Info.: 6th World Congress on Inflammation. Vancouver, British Columbia, Canada. August 02-06, 2003. International Association of Inflammation Societies. ISSN: 1023-3830.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 6 May 2004  
Last Updated on STN: 6 May 2004

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NEWS	25	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected
NEWS EXPRESS			FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT <a href="http://download.cas.org/express/v8.0-Discover/">http://download.cas.org/express/v8.0-Discover/</a>
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L2 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2005:370942 CAPLUS  
DOCUMENT NUMBER: 142:428778  
TITLE: Antibodies for inhibiting blood coagulation  
INVENTOR(S): Jiao, Jin-An; Wong, Hing C.; Wen, Jinghai  
PATENT ASSIGNEE(S): Sunol Molecular Corporation, USA  
SOURCE: U.S. Pat. Appl. Publ., 36 pp., Cont.-in-part of U.S.  
Ser. No. 293,417.  
CODEN: USXXCO

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005089929	A1	20050428	US 2003-618338	20030711
US 5986065	A	19991116	US 1997-814806	19970310
US 2002168357	A1	20021114	US 1999-293854	19990416
US 6555319	B2	20030429		
US 2003082636	A1	20030501	US 2002-293417	20021112
US 2005271664	A1	20051208	US 2005-87528	20050322
PRIORITY APPLN. INFO.:			US 1997-814806	A1 19970310
			US 1999-293854	A1 19990416
			US 2002-293417	A2 20021112

AB The authors disclose antibodies that provide superior anti-coagulant activity by binding native human TF with high affinity and specificity. Also disclosed are methods of using such antibodies to reduce cancer cell tissue factor activity and to detect cancer cells that express TF.

=> dis ibib abs 2-3

L2 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 2003:356462 CAPLUS  
 DOCUMENT NUMBER: 138:384144  
 TITLE: Humanized mouse anti-human tissue factor antibodies and fragments for diagnosis and treatment of blood coagulation-related diseases  
 INVENTOR(S): Jiao, Jian-An; Wong, Hing C.; Nieves, Esperanza Liliana; Mosquera, Luis A.  
 PATENT ASSIGNEE(S): Sunol Molecular Corporation, USA  
 SOURCE: PCT Int. Appl., 110 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037911	A2	20030508	WO 2002-US34727	20021029
WO 2003037911	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
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US 2003109680	A1	20030612	US 2001-990586	20011121
CA 2465325	AA	20030508	CA 2002-2465325	20021029
EP 1446157	A2	20040818	EP 2002-793851	20021029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
CN 1599624	A	20050323	CN 2002-824258	20021029
JP 2006503541	T2	20060202	JP 2003-540192	20021029
US 2006039901	A1	20060223	US 2005-122622	20050505
PRIORITY APPLN. INFO.:			US 2001-343306P	P 20011029
			US 2001-990586	A 20011121



AB The invention includes antibodies that provide superior anti-coagulant activity by binding native human TF with high affinity and specificity. Antibodies of the invention can effectively inhibit blood coagulation in vivo. Antibodies of the invention can bind native human TF, either alone or present in a TF:FVIIa complex, effectively preventing factor X or FIX binding to TF or that complex, and thereby reducing blood coagulation. Preferred antibodies of the invention specifically bind a conformational epitope predominant to native human TF, which epitope provides an unexpectedly strong antibody binding site. Also provided are humanized antibodies and fragments thereof that bind to the TF. The humanized antibodies and fragments are therefore can be used for treating tissue factor-related diseases involving blood coagulation, angiogenesis, tumor metastasis and inflammation.

L2 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:737410 CAPLUS

DOCUMENT NUMBER: 139:259967

TITLE: Anti-human tissue factor antibodies for treating thrombosis

INVENTOR(S): Jiao, Jin-an; Wong, Hing C.; Nieves, Esperanza Liliana; Mosquera, Luis A.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 43 pp., Cont.-in-part of U. S. Ser. No. 990,586.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003176664	A1	20030918	US 2002-310113	20021204
US 2003109680	A1	20030612	US 2001-990586	20011121
CN 1599624	A	20050323	CN 2002-824258	20021029
US 2006039901	A1	20060223	US 2005-122622	20050505
PRIORITY APPLN. INFO.:			US 2001-343306P	P 20011029
			US 2001-990586	A2 20011121

AB Disclosed is a method for preventing or treating thrombosis in a mammal such as a primate and particularly a human patient. A preferred method includes administering to the mammal a therapeutically effective amount of at least one humanized antibody, chimeric antibody, or fragment thereof that binds specifically to human tissue factor (TF). Addnl. methods and kits are provided.

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